A Phase 1b, Multicenter, Open-Label, Safety, Tolerability, and Activity Study of SYNT001 in Subjects with Chronic Pemphigus (Vulgaris or Foliaceus)

Unique Protocol ID: SYNT001-103

NCT Number: NCT03075904

Date of Protocol: 18 September 2018

1. PROTOCOL AND AMENDMENTS

- SYNT001-103 Protocol Version 1, 18 January 2017
- SYNT001-103 Protocol Amendment 1.1, 21 March 2017
- SYNT001-103 Protocol Amendment 1.1 SOC, 21 March 2017
- SYNT001-103 Protocol Amendment 2.0, 12 April 2017
- SYNT001-103 Protocol Amendment 2.0 SOC, 12 April 2017
- SYNT001-103 Administrative Letter 1.0, 10 May 2017
- SYNT001-103 Administrative Letter 2.0, 11 August 2017
- SYNT001-103 Administrative Letter 3.0, 21 September 2017
- SYNT001-103 Protocol Amendment 3.0, 10 October 2017
- SYNT001-103 Protocol Amendment 3.0 SOC, 10 October 2017
- SYNT001-103 Administrative Letter 4.0, 02 March 2018
- SYNT001-103 Protocol Amendment 4.0, 08 June 2018
- SYNT001-103 Protocol Amendment 4.0 SOC, 08 June 2018
- SYNT001-103 Protocol Amendment 5.0, 18 September 2018
- SYNT001-103 Protocol Amendment 5.0 SOC, 18 September 2018

Syntimmune, Inc.

CLINICAL STUDY PROTOCOL

A Phase 1b, Multicenter, Open-Label, Safety, Tolerability, and Activity Study of SYNT001 in Subjects with Chronic Pemphigus (Vulgaris or Foliaceus)

Protocol Number: SYNT001-103

IND Number: 132727

Study Drug: SYNT001

Sponsor: Syntimmune, Inc.

257 Park Avenue South

15th Floor

New York, NY 10010

PPD **Medical Monitor:**

43 Thorndike Street, Cambridge, MA 01240

Phone: PPD extensionPPD

Mobile: PPD

Original Protocol: 18 January 2017

Confidentiality Statement

The information contained herein is confidential and the proprietary property of Syntimmune, Inc. and any unauthorized use or disclosure of such information without the prior written authorization of Syntimmune is expressly prohibited.

SPONSOR SIGNATURE

I have read and approve this protocol. My signature, in conjunction with the signature of the Investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonisation Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), and the ethical principles that have their origins in the Declaration of Helsinki.

PPD	
	25/01/2017
	Date of Signature (DD Mm YYYY)

PROCEDURES IN CASE OF EMERGENCY

Serious Adverse Events

Any death, serious adverse event (SAE)* occurring in a subject while receiving study drug or within 7 days of receiving study drug, even though the event may not appear to be study drug related, must be promptly reported (within 24 hours) by telephone or electronic communication to the sponsor (or designee).

Emergency Contact Information

For SAE reporting:		For any other questions or to contact the Medical Monitor:						
Medpace Clinical Safety Medpace SAE hotline: Telephone: PPD PPD dial PP	dialP or PPD	PPD PPD Mobile phonePP Office phone:	D	ext.PPD				
Facsimile: PPD	or PPD							

SAE CRITERIA

- * A <u>serious adverse event</u> (SAE) is any untoward medical occurrence that at any dose results in any of the following outcomes, regardless of relationship to study drug (see <u>Section 11.3.1</u>, Serious Adverse Events for additional information):
 - Death
 - Life-threatening adverse drug event
 - Inpatient hospitalization or prolongation of existing hospitalization
 - A persistent or significant disability/ incapacity
 - A congenital anomaly/birth defect
 - An important medical event that may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

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INVESTIGATOR SIGNATURE

I have read and approve this protocol. My signature, in conjunction with the signature of the sponsor, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonization Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), and the ethical principles that have their origins in the Declaration of Helsinki.

Nothing in this document is intended to limit the authority of a physician to provide emergency

edical care under applicable regulations.	
nvestigator Signature	Date of Signature (DD Mm YYYY)
ame of Investigator (please print)	

1 SYNOPSIS

Study title	A Phase 1b, Multicenter, Open-Label, Safety, Tolerability, and Activity Study of SYNT001 in Subjects with Chronic Pemphigus (Vulgaris or Foliaceus)				
Protocol number	SYNT001-103				
Number of study centers	Approximately 10 (US)				
Clinical phase	Phase 1b				
Study background	SYNT001, a humanized, affinity-matured IgG4-kappa monoclonal antibody (mAb), blocks IgG and IgG immune complex (IC) interactions with the neonatal Fc receptor (FcRn) and thereby the major functions of FcRn in protecting IgG and IgG immune complexes from degradation and their role in downstream signaling events. Specific and high affinity blockade of FcRn with SYNT001 has been shown to increase the catabolism of IgG and IgG IC in healthy volunteers. This predicts that SYNT001 will also accelerate degradation of endogenous circulating IgG autoantibodies and IgG-antigen IC specifically involved in the pathogenesis of autoimmunity. Blocking FcRn interactions with IgG containing immune complexes further predicts that SYNT001 will have consequences for innate and adaptive cellular immunity. In the first instance, blocking multimeric IgG IC interactions with FcRn within antigen presenting cells will result in inhibition of IC-stimulated inflammatory cytokine production and release by these cells. In addition, as FcRn determines the intracellular itinerary of IgG immune complexes within and among compartments important in cellular immunity, it is further anticipated that SYNT001 will block antigen processing and presentation of antigens contained within IC that otherwise lead to CD8+ and CD4+ T cell activation. Thus, SYNT001 will specifically target immune functions associated with IgG and IC that are involved in many autoimmune conditions and dismantle their ability to cause disease. SYNT001 targets mechanisms contributing to pathology in a variety of IgG-mediated autoimmune disorders, including warm antibody autoimmune hemolytic anemia (WAIHA), pemphigus, and chronic inflammatory demyelinating polyneuropathy (CIDP). While current treatments for certain autoimmune disorders including chronic steroids, immunosuppressants, intravenous immunoglobulin (IVIG), plasmapheresis, and anti-CD20 monoclonal antibodies (mAbs), such as rituximab, can be effective, they are frequently associated with significant adverse effects, a				
	Pemphigus is a rare group of blistering autoimmune diseases that affect the skin and mucous membranes. Autoantibodies are thought to play an important				

Study rationale	pathogenic role in the mucosal and cutaneous manifestations in patients with pemphigus. Administration of SYNT001, leading to a significant decrease in total IgG, and thereby a corresponding decrease in the level of the pathogenic autoantibodies as well as the ICs to which they are associated, should lead to a decrease in the mucosal and cutaneous manifestations in subjects with pemphigus. Moreover, the ability of SYNT001 to reduce circulating immune complexes (CICs) and the associated innate and adaptive immune responses may allow for further sustained disease modification. This study is being conducted to further evaluate the safety, tolerability,						
	pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity of intravenous (IV) SYNT001 as well as its effects on pemphigus disease activity markers.						
Study objectives	Primary objective						
	To evaluate the safety and tolerability of 5 once-weekly IV infusions of SYNT001 at different dose levels in subjects with chronic pemphigus (vulgaris or foliaceus)						
	Secondary objectives						
	To determine the PK of SYNT001 following 5 once-weekly 1-hour IV infusions at different dose levels						
	• To assess the effect of 5 once-weekly doses of SYNT001 at different dose levels on the following PD biomarkers:						
	 Immunoglobulins: IgG, IgG subtypes (IgG1-4), IgA, IgM 						
	o Albumin						
	To assess the effect of 5 once-weekly doses of SYNT001 at different dose levels on the following disease activity markers:						
	o Serum anti-desmoglein (Dsg) (1 and 3) antibody levels						
	o Pemphigus Disease Area Index (PDAI)						
	To assess immunogenicity (anti-SYNT001 antibodies)						
	Exploratory objectives						
	To assess the effect of 5 once-weekly doses of SYNT001 at different dose levels on the following biomarkers, including:						
	 Serum anti-epithelial cell antibody (AECA) levels by indirect immunofluorescence 						
	Circulating immune complexes (CIC)						
	o Complement component 3 (C3)						
	 Exploratory biomarkers (FCGR2A (single nucleotide polymorphism- SNP), RNAseq, urine IgG) 						

Immune phenotyping by flow cytometry for CD3⁺CD4⁺ T, CD3⁺CD8⁺ T, monocytes, NK cells and B cells

- SYNT001 levels in skin biopsies (optional)
- To characterize corticosteroid use during the study

Study design

Phase 1b, multicenter, open-label, safety, tolerability, and activity study

Methodology

Two cohorts of 8 eligible subjects each will receive 5 once-weekly 60-minute infusions of SYNT001 in planned doses of 10 mg/kg or 30 mg/kg. Based on review of safety, PD, and clinical outcomes of these 2 cohorts, a third cohort of up to 8 subjects may be treated at another dose, with a maximum dose of 45 mg/kg, but may also be lower than 10 mg/kg or between 10 and 30 mg/kg, inclusive.

Cohort	No. of subjects	Dose
1	8	SYNT001 10 mg/kg
2	8	SYNT001 30 mg/kg

Cohorts will be dosed sequentially beginning with Cohort 1. The first 2 subjects will be dosed at least 24 hours apart. A review of the 24-hour safety data for the first subject will be performed to ensure that there are no overt safety concerns before dosing the second subject. A review of the 7-day safety data for the first 2 subjects will be performed prior to dosing the remaining 6 subjects in the cohort. This evaluation will include a review of AE/SAE reports, vital sign assessments, physical examinations, ECGs, and clinical laboratory testing. The seriousness, severity, and relatedness of AEs/SAEs will also be considered in the safety evaluation. Safety data will be reviewed on a continuous basis throughout the study. All safety data and any available and relevant PD data through Day 42 (2 weeks after the last subject's last dose in Cohort 1) will be reviewed by a dose escalation committee before Cohort 2 is initiated. Escalation to Cohort 2 will proceed if there are no concerning safety signals and the review of available and relevant PD data supports advancing to a higher dose. The dose for Cohort 2 will be finalized after review of the safety and PD data, but will not exceed 30 mg/kg. Cohort 2 and Cohort 3, if added, will be dosed per the same schedule as Cohort 1.

On days where study drug is administered, vital sign and pulse oximetry measurements will be collected immediately prior to the infusion; 15, 30, and 45 minutes after the start of the infusion; at completion of the infusion; and 30 minutes, 1 hour and 2 hours following completion of the infusion.

On Days 0 and 28, PK blood samples will be collected prior to infusion start and then over the subsequent 48 hours. Subjects will remain at the clinic through the 6-hour PK sample collection and will return to the clinic for the 24- and 48-hour collections. Additional samples will be collected on Days 5 and 33.

On Day 0 photographs will be taken of active lesions. Follow-up photographs will be taken of the same areas on Days 33 and 56. If a subject begins a steroid taper, additional photographs will be taken at the clinic visit during which the decision to begin the taper is made.

Subsequent visits will occur on Days 1, 2, 5, 7, 12, 14, 19, 21, 28, 29, 30, 33, and 42 for safety assessments, study drug dosing, sample collections, and other study procedures.

Subjects also will return to the clinic on Day 56 (28 days after receiving their last dose of study drug) for an End-of-Study/Follow-Up visit.

See Table 1 for a schedule of all study events. To assess safety and tolerability, subjects will undergo physical examinations (PEs; including weight), vital sign measurements, clinical (safety) laboratory tests, adverse event (AE) assessments, concomitant medication assessments, and electrocardiograms (ECG).

Number of subjects

Approximately 16; two cohorts of 8 subjects each. An additional cohort of up to 8 subjects may be enrolled. Subjects who withdraw for any reason other than an AE and who do not receive study drug or have only received one dose of study drug may be replaced, up to one subject per cohort. The maximum number of subjects who may be enrolled in this study is 27 (24 + up to 3 replacements, as necessary). Within each dosing cohort, no more than 3 subjects with pemphigus foliaceus may be enrolled.

Diagnosis and main entry criteria

Inclusion criteria:

Subjects must meet the following criteria to be included:

- 1. Willing and able to read, understand and sign an informed consent form;
- 2. Male or female \geq 18 years of age at the time of screening;
- 3. Documented diagnosis of pemphigus vulgaris or foliaceus based on all 3 of the following criteria:
 - a. Documented clinical history consistent with pemphigus vulgaris or foliaceus (clinical presentation defined as mucosal and/ or skin lesions);
 - b. Presence of Anti-Dsg 1 or 3 antibodies above the upper limit of normal:
 - c. History of at least one positive tissue-based test (e.g., biopsy, direct immunofluorescence [DIF])
- 4. Active disease: Lesions lasting > 2 weeks, and 3 active lesions in skin or mucosa or 2 active lesions with at least one being a skin lesion > 1 cm diameter:
 - a. If treated with rituximab or other anti-CD20 antibodies, last dose
 12 months prior to screening;

- If being treated with other immunosuppressants (i.e., azathioprine, mycophenolate mofetil or cyclosporine), must be on stable dose
 (< 10% change in dose) for 6 weeks prior to screening;
- c. If being treated with corticosteroids, must be $\leq 1 \text{mg/kg/day}$ and stable (< 10% change in dose) for 2 weeks prior to screening;
- d. Allowed topical therapies for pemphigus lesions upon entering the study include petroleum jelly or Aquaphor® for the skin or chlorhexidine for the mouth
- 5. Body mass index (BMI) $18.5 35.0 \text{ kg/m}^2$;
- 6. Has a negative urine pregnancy test (for women of childbearing potential) documented prior to the first dose of study drug;
- 7. Females of childbearing potential must agree to be abstinent or else use any two of the following medically acceptable forms of contraception (<1% per year failure rate) from the Screening Period through 60 days after the final study dose: oral contraceptive, condom with or without spermicidal jelly, diaphragm or cervical cap with spermicidal jelly, or intra-uterine device (IUD). A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception.
- 8. Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months do not require contraception during the study.
- 9. Males with female partners of childbearing potential, including males who are surgically sterile (post vasectomy), must agree to be abstinent or else use a medically acceptable form of contraception from the screening period through 60 days after the final study dose.

Exclusion criteria:

Subjects meeting any of the following criteria are to be excluded:

- 1. Subject unable or unwilling to comply with the protocol;
- Active non-hematologic malignancy or history of non-hematologic malignancy in the 3 years prior to screening (exclusive of non-melanoma skin cancer and cervical cancer in situ);
- 3. Positive for HIV or hepatitis C antibody;
- 4. Positive for hepatitis B surface antigen;
- 5. Active infection or history of recurrent infections;
- 6. IVIG use within 60 days of screening;
- 7. Received any cytotoxic (other than azathioprine) or mAb therapy in the 3 months prior to screening;
- 8. Any exposure to an investigational drug or device within the 30 days prior to screening
- 9. Plasmapheresis or immunoadsorption within 60 days of screening

	10. Cellular therapy at any time prior to screening
	11. Use of any immunosuppressive drugs apart from corticosteroids,
	azathioprine, mycophenolate mofetil, or cyclosporine within 3 months of
	screening
	12. Serum total IgG < 600 mg/dL;
	13. Subject has any current medical condition that, in the opinion of the
	Investigator, may compromise their safety or compliance, preclude
	successful conduct of the study, or interfere with interpretation of the results
	(e.g., a significant pre-existing illness or other major comorbidity that the
	Investigator considers may confound the interpretation of the study results);
	14. Any vaccination within 2 weeks of screening
Study drug, dosage,	SYNT001
and administration	
	Doses: 10 mg/kg and 30 mg/kg. A third cohort of up to 8 subjects may be treated
	at another dose, with a maximum dose of 45 mg/kg, but may also be lower than 10 mg/kg or between 10 and 30 mg/kg, inclusive.
	SYNT001 is provided as a liquid at a nominal concentration of 50 mg/mL.
	SYNT001 is diluted in Dextrose 5% in Water (D5W) to prepare the solution for
	infusion.
	Route of administration: IV in 250 mL over 1 hour
Control, dose, and	Not applicable
route of	
administration	
Duration of subject	Up to 70 days (10 weeks): Screening of up to 2 weeks (14 days); dosing period
participation and	of 4 weeks (28 days); and 4 weeks (28 days) of follow-up
duration of study	

Prohibited Concomitant treatments

All treatments a subject receives within 14 days prior to enrollment through the end of the study (Day 56) will be documented. Concomitant medication and treatment for co-existing conditions, including those for pemphigus, are permitted if not excluded below. Topical antibiotics are permitted to treat active infections that occur on study. Topical or systemic treatments for oral candidiasis are permitted. Topical lidocaine for transient pain relief is acceptable as needed. Significant increases in anti-pemphigus medications may result in subjects being discontinued from the study. Concomitant treatment that is medically indicated for any AEs the subject experiences during the study are permitted.

Use of the following medications will not be permitted during the study unless otherwise specified:

- Rituximab or other anti-CD20 antibody
- Monoclonal antibodies other than study drug
- Any immunosuppressive drugs apart from corticosteroids, azathioprine, mycophenolate mofetil, or cyclosporine
- Topical steroids
- Any dietary herbal supplements
- Any investigational drug or device
- Any vaccinations

If over a period of at least two weeks on study drug, a subject on corticosteroids shows the absence of new lesions and significant healing of lesions that existed at study baseline, a slow corticosteroid taper may be started as per the following suggested schedule

- If on > 30 mg of prednisone per day, decrease by 10 mg every two weeks until a dose of 30 mg per day then decrease by 5 mg every two weeks
- If on < 30 mg of prednisone per day, decrease by 5 mg every two weeks

Safety assessments

Safety assessments include AEs, serious adverse events (SAEs), PEs, vital sign measurements, clinical safety laboratory evaluations, ECGs, and reasons for treatment discontinuations due to toxicity. Safety assessments will be performed at specified time points and prior to discharge from the clinic. Vital sign measurements, including blood pressure, pulse rate, respiratory rate, and temperature will be monitored throughout the study. Pulse oximetry will be monitored during the study drug infusion and for 2 hours following the end of the infusion.

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; Version 4.03) will be used for grading clinical and laboratory AEs.

	The AE reporting period for a subject enrolled in the study begins when the subject provides informed consent and is continued for 28 days after the last dose of study drug. All AEs that occur in the enrolled subjects during the AE reporting period must be recorded, regardless of the relationship of the AE to study drug. Any known untoward event that occurs beyond the AE reporting period that the Investigator assesses as related to study drug should also be recorded.
Dose-escalation rules	Dose-limiting toxicity (DLT) will be defined generally as clinically significant, severe (Grade 3) AEs occurring in ≥ 2 subjects that are determined to be clinically significant and considered related to study drug. If 2 or more subjects at any time in any cohort (8 total subjects per cohort) have Grade 3 AEs that are determined to be clinically significant and considered to be related to study drug, dosing will be halted within that cohort and no further dose-escalation will occur. If the dose-escalation stopping rule is met in Cohort 1 (10 mg/kg) all safety data and all available pharmacodynamics data will be reviewed and a cohort may be added at a dose at least 50% lower than the 10 mg/kg dose. If the stopping rule is not met after Cohort 1 (10 mg/kg), dose-escalation may proceed up to a maximum of 30 mg/kg. If the dose-escalation stopping rule is met in Cohort 2, all safety data and all available pharmacodynamics data will be reviewed and a cohort may be added at a dose at least 30% lower than the Cohort 2 dose. If the stopping rule is not met after Cohort 2, dose-escalation may proceed up to a maximum of 45 mg/kg; however, this cohort may also receive a dose equal to or less than 30 mg/kg based on evaluation of all safety and pharmacodynamic data.
Study stopping rule	If any subject experiences a life-threatening AE (Grade 4) that is considered to be related to study drug, any further dosing in all enrolled subjects will be suspended until the DEC has evaluated the event and determined the next appropriate course of action. At any time during the study, the study may be discontinued if the DEC determines that further drug exposure would pose an undue risk to subjects.
Individual stopping rule	Dosing for any individual subject will be discontinued (i.e., further treatment with the study drug will not be given) if the subject experiences any study drug-related SAE or any study drug-related non-SAE adverse event that, in the judgement of the Investigator and Medical Monitor, suggest that it could be unsafe to administer further study drug to that subject. Additionally, a subject may be discontinued from further treatment with study drug, at the discretion of the Investigator with consultation with the Medical Monitor, if they require a

	significant increase in dose(s) of anti-pemphigus medication(s) for the management of pemphigus.						
Pharmacokinetics	The PK of SYNT001 will be evaluated following the first and last (fifth) doses of SYNT001. Starting on Days 0 and 28, serum samples will be collected just prior to the start of study drug infusion (pre-dose), at 5 minutes and 2, 4, 6, 24, and 48 hours after the end-of-study drug infusion. Additional samples will be collected on Days 5 and 33. Study drug concentration will be used to calculate the following PK parameters: $C_{1/2}$, C_{max} , C						
Pharmacodynamics/ Activity	PD samples will be collected for analysis of IgG (serial assessment of IgG levels to identify C _{min} , T _{min}); IgG1-4 subtype levels; IgA levels; IgM levels; albumin levels; anti-Dsg (1 and 3) antibody levels; serum AECA by direct immunofluorescence; CIC; C3; exploratory biomarkers (<i>FCGR2A</i> SNP, RNAseq, urine IgG, CD3 ⁺ CD4 ⁺ T, CD3 ⁺ CD8 ⁺ T, monocytes, NK cells and B cells).						
Immunogenicity	Up to 4 samples will be collected for immunogenicity analyses. Samples will be collected on Days 0 (pre-dose), 14, 28, and 56.						
Skin biopsy	Optional skin biopsy samples will be collected on Day 0 pre-dose and on Days 1, 2, 14, 33 and 56 to analyze SYNT001 levels.						
Photography	Photographs of active lesions will be taken at Day 0. Follow-up photographs of the same areas will be taken on Days 33 and 56. Subjects who begin a steroid taper will have additional photographs taken at the clinic visit during which the decision to begin the taper is made.						
Statistical methods	Sample size consideration						
	Formal sample size calculations were not performed. The number of subjects was chosen based on feasibility and was considered sufficient to meet the study objectives.						
	Data presentations/Descriptive statistics						
	Three populations will be employed in the analysis of study data.						
	The intent-to-treat (ITT) population will consist of all subjects who have received at least one dose of study drug. All safety analyses will be performed on the ITT population.						
	 The PK population will consist of all subjects who receive at least one dose of study drug and have sufficient post-dose blood samples to obtain PK parameters. 						

• The PD population will consist of all subjects who receive at least one dose of study drug and have post-dose PD data available.

Primary safety analyses will be performed on the ITT population. Demographics, subject disposition, and screening and baseline characteristics will be summarized for the PK and ITT populations, where appropriate.

Criteria for evaluation

Objective	Endpoint					
Primary						
Safety and tolerability of 5 once- weekly IV infusions of SYNT001 to subjects with pemphigus vulgaris or foliaceus	AEs and clinical (safety) laboratory tests					
Secondary						
PK of SYNT001 following a 1-hour IV infusion	PK parameters: $t_{1/2}$, C_{max} , T_{max} , $AUC_{0\text{-}24}$, and $AUC_{0\text{-}\infty}$.					
Effect of 5 once-weekly IV doses of SYNT001 on: • Total IgG (IgG1-4), IgA, IgM, and albumin • Serum anti-Dsg (1 and 3) antibodies	Changes in levels of IgG, IgG subtypes (IgG1-4), IgA, IgM, albumin, serum anti-Dsg (1 and 3) antibodies					
Assess immunogenicity	Anti-SYNT001 antibodies					
Disease Activity	PDAI Scores					
Exploratory						
Effect of 5 once-weekly IV doses of SYNT001 on biomarkers including: • CIC • C3 • Serum anti-epithelial cell antibody (AECA) levels • Exploratory biomarkers (FCGR2A SNP, RNAseq, urine IgG) • Immune phenotyping by flow cytometry	Changes in CIC; C3; AECA levels by indirect immunofluorescence; FCGR2A SNP; RNAseq; urine IgG, CD3+CD4+ T, CD3+CD8+ T, monocytes, NK cells and B cells; urine IgG levels; changes in blood transcriptome					
Concomitant Treatment	Corticosteroid use during the study					
SYNT001 levels in skin biopsies	Measures of SYNT001 levels in skin biopsies					

Treatment-emergent AEs (TEAEs) will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA®; Version 19 or higher) System Organ Class (SOC) and preferred term, classified from verbatim terms. The incidence and percentage of subjects with at least 1 occurrence of a preferred

term will be included, using the most severe grade. The number of events per preferred term will also be summarized. Causality (relationship to study treatment) will be summarized separately.

TEAEs, SAEs, and AEs leading to withdrawal, or treatment discontinuation will be listed by subject, and cohort using SOC and preferred terms. Duration of AEs will be determined and included in listings, along with action taken, and outcome.

Laboratory results will be summarized by time point and cohort. The incidence of laboratory abnormalities will be summarized. The worst on-study grade after the first dose of study drug will be summarized. Results for variables that are not coded will be presented in the listings as below, within, and above the normal limits of the central laboratory. Vital sign measurements will be summarized by cohort at each scheduled time point using descriptive statistics.

Study drug concentrations will be used to calculate the following PK parameters: $t_{1/2}$, C_{max} , T_{max} , and area under the curve (AUC). PK parameters will be determined using non-compartmental method(s). Descriptive statistics of PK parameters for SYNT001 will include mean, standard deviation (SD), coefficient of variation (CV), median, minimum, and maximum. T_{max} will be reported as median and range. All descriptive statistics will be performed on untransformed PK parameters and after log_{10} transformation of PK parameters.

PD results will be summarized by cohort. Descriptive statistics of PD parameters for SYNT001 will include mean, SD, CV, median, minimum, and maximum.

Immunogenicity results will be summarized by cohort. Descriptive statistics will include mean, SD, CV, median, minimum, and maximum.

Table 1: Study Assessments

Timepoint (Study Day)	Screen -14 to -1	0	1 (±1 hr)	2 (± 2 hr)	5 ^p (±4 hr)	7 (±4 hr)	12 ^p (±6 hr)	14 (±6 hr)	19 ^p (±6 hr)	21 (±6 hr)	28 (±6 hr)	29 (±1 hr)	30 (±2 hr)	33 (±4 hr)	42 (±3 day)	Follow-Up 56 (±5 days) or ET Visit	Extended Follow- up ^q
Informed Consent	X																
Demographics/Medical History	X																
Inclusion/Exclusion	X																
Physical Examination ^a	X	X				X		X		X	X				X	X	
Vital Signs ^b	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pulse Oximetry ^c		X				X		X		X	X						
Clinical Safety Labs ^d	X	X				X		X		X	X			X	X	X	
Pregnancy test ^e	X	X														X	
Hepatitis & HIV Screen	X																
12-Lead ECG ^f	X	X					X				X					X	
Tetanus & VZV antibodies ^g		X														X	X
PDAI Score		X				X		X		X	X			X	X	X	
PK Sampling ^h		X	X	X	X						X	X	X	X			
Immunogenicity ⁱ		X						X			X					X	
Study Drug Administration ^j		X				X		X		X	X						
Immunoglobulins (IgG, IgA, IgM) and IgG subtypes (IgG 1-4) ^k	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CIC		X			X	X	X	X	X	X	X			X	X	X	
Anti-Dsg (1 & 3) antibody titer	X	X				X		X			X			X		X	
C3 and AECA ¹		X						X						X		X	
FCGR2A ^m		X															
RNAseq ^m		X						X						X		X	
Urine IgG ^m	_	X						X						X		X	_
Immune phenotyping ⁿ		X									X						
Optional Skin Biopsy		X	X	X				X						X		X	
Photography ^o		X												X		X	
Adverse Events		To be collected from the date that the ICF is signed until 28 days after last dose of study drug.															
Concomitant Medications		To be collected from within 14 days prior to Day 0 through 28 days after last dose of study drug.															

Concomitant Medications

To be collected from within 14 days prior to Day 0 through 28 days after last dose of study drug.

ECG = electrocardiogram; ET= Early Termination; HIV = human immunodeficiency virus; ICF = informed consent form; PD = pharmacodynamic; PK = pharmacokinetic; VZV = varicella-zoster virus

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- a: Complete PE, including weight, to be performed. Height and BMI will be additional assessments conducted at screening.
- b: **Vital sign** measurements (sitting blood pressure, heart rate, respiratory rate, and oral temperature) to be obtained after 5 minutes of seated rest. Any abnormal measurements are to be repeated after 5 minutes of rest. On Days 0, 7, 14, 21, and 28 vital sign measurements will be collected immediately prior to the infusion; 15, 30, and 45 minutes after the start of the infusion; at completion of the infusion; and 30 minutes, 1 hour and 2 hours following completion of the infusion.
- c: **Pulse oximetry:** On Days 0, 7, 14, 21, and 28, pulse oximetry to be measured immediately prior to the infusion; 15, 30, and 45 minutes after the start of the infusion; at completion of the infusion; and 30 minutes, 1 hour and 2 hours following completion of the infusion.
- d: Clinical safety labs: hematology, clinical chemistry, and urinalysis (see Section 6.7 for a complete list). Full clinical safety lab draws will be collected at Screening and on Days 0, 7, 14, 21, 28, 33, 42 and 56.
- e: **Pregnancy test:** To be performed at time of screening and prior to first dose of SYNT001 on Day 0 and on Day 56 (urine or serum test is acceptable, however, positive urine tests must be confirmed with serum testing.)
- f: Digital 12-lead ECG to be obtained after 5 minutes of rest in the supine position and in triplicate at least 1-2 minutes apart (see Section 6.6 for additional information). On Days 0 and 28 to be obtained 5 minutes after the completion of infusion. Day 12 ECG will be collected only if the visit is conducted at the study site.
- g: **Serology**: Testing at Day 56 will not be done for any subject whose baseline titer is below the level of detection. If the Day 56 results are greater than 30% below the baseline value, or if the subject falls below the level of detection, the subject will be re-tested at 1 month after the Follow-Up visit (approximately 2 months after the subject's last dose); if still below the baseline value (or level of detection), the subject will be re-tested after another month (3 months after last dose). Any subject whose baseline value for tetanus or VZV was above the detectable level at baseline, and is not within 30% of the baseline value or is below the detectable level on Day 56 and upon 2 retests (2 and 3 months following last dose of SYNT001), will be referred to their primary care physician for further management. See Section 6.7.3 for additional information.
- h: **PK:** Starting on Days 0 and 28, serum samples will be collected just prior to the start of study drug infusion (pre-dose), and at 5 minutes and 2, 4, 6, 24, and 48 hours after the end-of-study drug infusion. Additional samples will be collected on Days 5 and 33. See Section 6.7.4 for additional information.
- i: Immunogenicity: Blood samples will be collected pre-dose when collected on dosing days. See Section 6.7.6 for additional information.
- j: Prior to **study drug infusion**, SYNT001 drug product is to be diluted in Dextrose 5% in Water (D5W) to a total volume of 250 mL and administered intravenously over 1 hour using a 0.2-micron, inline filter. See Section 9 for additional information.
- k: Immunoglobulins (IgG, IgA, IgM) and IgG subtypes (IgG 1-4): Collected for measurements of IgG, IgG subtypes (IgG1-4), IgA, and IgM at every visit. On Days 0, 7, 14, 21, and 28, samples are collected prior to infusion of study drug. See Section 6.7.5 for additional information
- 1: Exploratory PD samples (C3 and AECA): collected pre-dose when collected on dosing days. See Section 6.7.5 for complete information.
- m: Samples to be collected and stored; pending review of clinical and pharmacodynamics assessments
- n: Immune phenotyping by flow cytometry for measurement of CD3+CD4+T, CD3+CD8+T, monocytes, NK cells and B cells
- o: Photographs of active lesions taken prior to first dose on Day 0. Follow-up photographs will be taken at Days 33 and 56. Subjects who begin a steroid taper will have additional photographs taken at the clinic visit during which the decision to begin the taper is made.
- p: Visit Days 5, 12 and 19 may be conducted via at-home nursing in lieu of a subject visit to the study site.
- q: Extended follow-up visits will occur only if additional testing for anti-tetanus and/ or anti-VZV titers are required. These visits will occur as needed at approximately 2 months post last dose and 3 months post last dose.

Table 2: Timing Window Allowances for PK/PD Sampling, ECG, and Vital Sign Measurements

Pharmacokinetic and Pharmacodynamic Sampling	
Timepoint	Tolerance Window
0 hour	−240 min to 0 hour
5 minutes post end-of-infusion	± 5 minutes
2, 4, & 6 hours post end-of-infusion	± 15 minutes
24 hours post end-of-infusion	± 60 minutes
48 hours post end-of-infusion	± 120 minutes
ECG	
Timepoint	Tolerance Window
5 minutes post end-of-infusion	± 10 minutes
Vital Signs ^a	
Timepoint	Tolerance Window
0 hour	−240 min to 0 hour
15, 30, and 45 minutes after start of infusion	± 5 minutes
60 minutes after start of infusion	± 10 minutes
30, 60 and 120 minutes post end-of-infusion	± 10 minutes

a: Vital signs to include blood pressure, pulse rate, respiratory rate, oral temperature, and pulse oximetry.

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LIST OF ABBREVIATIONS

ADA Anti-drug antibodies

AE Adverse event

AECA Anti-epithelial cell antibody
ALT Alanine aminotransferase
ANA Antinuclear antibody
AST Aspartate aminotransferase
ATC Anatomical therapeutic chemical

AUC_{0.24} Area under the plasma concentration-time curve from pre-dose (time 0) to 24 hours post-dose

 $AUC_{0-\infty}$ Area under the plasma concentration-time curve from pre-dose (time 0) to infinity

BLQ Below the limit of quantification

BMI Body mass index
BUN Blood urea nitrogen

CAR-T Chimeric antigen receptor and T-cell

CFR Code of Federal Regulations
C3 Complement component 3
CBC Complete blood count

CIC Circulating immune complexes

CIDP Chronic inflammatory demyelinating polyneuropathy

C_{max} Maximum plasma concentration determined directly from the concentration-time profile

CRO Contract research organization

CV Coefficient of variation

CVID Common variable immune deficiency

DEC Dose escalation committee
D5W Dextrose 5% in Water
DIF Direct immunofluorescence
DNA Deoxyribonucleic acid
ECG Electrocardiogram

eCRF Electronic case report form
ESR Erythrocyte sedimentation rate
FcGR2a Fc Gamma R2a receptor
FcRn Neonatal Fc receptor

FDA Food and Drug Administration

GCP Good Clinical Practice

GI Gastrointestinal
HBV Hepatitis B virus
HCV Hepatitis C virus

HIPAA Health Insurance Portability and Accountability Act

HIV Human immunodeficiency virus

IB Investigator's brochure IC Immune complex

Pemphigus

ICF Informed consent form

ICH International Conference on Harmonization

IgA Immunoglobulin A
IgG Immunoglobulin G
IgG1-4 Immunoglobulin G1-G4
IgM Immunoglobulin M
IL-12 Interleukin 12

IND Investigational new drug
IRB Institutional review board

ITT Intent-to-treat
IUD Intrauterine devices

IV Intravenous

IVIG Intravenous immunoglobulin

MedDRA Medical Dictionary for Regulatory Activities

NHL Non-Hodgkin lymphoma
PD Pharmacodynamics
PE Physical examination
PK Pharmacokinetic
RBC Red blood cells
RNAseq RNA sequencing

QTcF Corrected QT interval using Fridericia's formula

SAE Serious adverse event
SAP Statistical analysis plan
SAS Statistical Analysis System

SD Standard deviation

SNP Single nucleotide polymorphism

SOC System Organ Class

SOP Standard operating procedures

SYNT001 A humanized, affinity matured IgG4-kappa monoclonal antibody

 $t_{1/2}$ Half-life

TEAE Treatment-emergent adverse event

T_{max} Observed time to reach peak plasma concentration

TNF Tumor necrosis factor ULN Upper limit of normal

UNS Unscheduled

VZV Varicella-zoster virus

WAIHA Warm antibody autoimmune hemolytic anemia

WHO World Health Organization

WHO-DD World Health Organization Drug Dictionary

2 BACKGROUND AND RATIONALE

SYNT001, a humanized, affinity-matured IgG4-kappa monoclonal antibody (mAb), blocks IgG and IgG immune complex (IC) interactions with the neonatal Fc receptor (FcRn) and thereby the major functions of FcRn in protecting IgG and IgG ICs from degradation and their role in downstream signaling events. Specific and high affinity blockade of FcRn with SYNT001 has been shown to increase the catabolism of IgG and IgG IC in healthy volunteers. This predicts that SYNT001 will also accelerate degradation of endogenous circulating IgG autoantibodies and IgG-antigen IC specifically involved in the pathogenesis of autoimmunity. Blocking FcRn interactions with IgG-containing ICs further predicts that SYNT001 will have consequences for innate and adaptive cellular immunity. In the first instance, blocking multimeric IgG IC interactions with FcRn within antigen-presenting cells will result in inhibition of IC-stimulated inflammatory cytokine production and release by these cells. In addition, as FcRn determines the intracellular itinerary of IgG ICs within and among compartments important in cellular immunity, it is anticipated that SYNT001 will block antigen processing and presentation of antigens contained within IC that otherwise lead to CD8⁺ and CD4⁺ T cell activation. Thus, SYNT001 will specifically target immune functions associated with IgG that are involved in certain autoimmune conditions and dismantle their ability to cause disease.

SYNT001 targets key mechanisms contributing to pathology in a variety of IgG-mediated autoimmune disorders, including warm antibody autoimmune hemolytic anemia (WAIHA), pemphigus, and chronic inflammatory demyelinating polyneuropathy (CIDP).

While current treatments for certain autoimmune disorders, including high-dose steroids, immunosuppressants, intravenous immunoglobulin (IVIG), plasmapheresis, and anti-CD20 monoclonal antibodies (mAbs), such as rituximab, can be effective, they are associated with significant adverse effects, as well as delayed or non-durable responses.

Pemphigus is a rare group of blistering autoimmune diseases that affect the skin and mucous membranes. Autoantibodies have been shown to play an important pathogenic role in the mucosal and cutaneous manifestations in patients with pemphigus. Administration of SYNT001, which significantly decreases total IgG, including a corresponding decrease in the level of the pathogenic autoantibodies and the ICs to which they are associated, may lead to a decrease in the mucosal and cutaneous manifestations in patients with pemphigus. Moreover, the ability of SYNT001 to reduce circulating immune complexes (CICs) and the associated innate and adaptive immune responses may allow for further sustained disease modification.

2.1 Study Rationale

This study is being conducted to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity of intravenous (IV) SYNT001 as well as its effects on pemphigus disease activity markers.

2.2 Selection of Doses in this Study

The planned dose levels of SYNT001 for this Phase 1b safety and proof-of-concept study of 10 mg/kg and 30 mg/kg were selected from careful review of the safety, tolerability, and PD effect on total IgG levels after single and repeat dosing of SYNT001 in non-human primates (NHPs), as well as the safety, tolerability, and PD effect on total IgG levels after single ascending doses of SYNT001 in healthy volunteers. In addition, further consideration was given to the desired level of FcRn blockade to achieve suppression of IgG to a range that has been previously correlated with disease remission. Further, we considered the potential effects of inhibiting FcRn function as they relate to immune complex associated innate and adaptive immunity in choosing these dose levels based upon exploratory studies of a single ascending dose of SYNT001 in healthy volunteers. From the NHP studies, single doses of SYNT001 produced a dose-dependent decrease in total IgG and a further decrease was seen with repeated weekly doses up to a maximum 70% reduction at 100 mg/kg. This magnitude of total IgG reduction is approaching the expected maximal effect of 100% inhibition of FcRn function based on murine studies also performed by Syntimmune and others [Roopenian 2003, Nixon 2015]. In the recently completed Phase 1a trial with SYNT001 in healthy volunteers a single dose caused a maximum average 50% drop in total IgG with IV dosing at 30 mg/kg. Based on the NHP studies further reductions are expected following multiple dosing. A comparable decrease in pathogenic autoantibodies is also anticipated.

In the NHP studies, relevant adverse effects, mild-to-moderate infusion reactions, were observed only after the third weekly IV administration, concurrent with the development of anti-SYNT001 antibodies. In the recently completed Phase 1a healthy male volunteer study, the doses of SYNT001 up to and including 30 mg/kg have been well tolerated. There were no dose limiting toxicities, serious adverse events, or any other safety concerns identified. No AEs were observed in the 1 and 3 mg/kg dose cohorts. A single Grade 2 AE was observed; a headache in the 10 mg/kg cohort, treated with acetaminophen. Other subjects had mild (Grade 1) AEs at 10 mg/kg. In Cohort 4 (30 mg/kg), 5 subjects received SYNT001. All five subjects experienced AEs; all were mild (Grade 1), transient and resolved spontaneously without intervention. Therefore, it is anticipated that the doses selected for this study should be well tolerated and have clinically relevant PD effects in patients with chronic pemphigus (vulgaris or foliaceus). For a summary of

findings from the single dose, clinical study in healthy subjects and further details on the nonclinical findings, please refer to the SYNT001 Investigator's Brochure.

2.3 Compliance Statement

This study will be conducted in compliance with Good Clinical Practice (GCP), including the International Conference on Harmonisation (ICH) Guidelines and FDA regulations, consistent with the principles outlined in the Declaration of Helsinki. In addition, the Investigator agrees to adhere to all applicable local laws and regulatory requirements relevant to the use of new therapeutic agents.

The study will be conducted in compliance with the protocol. The appropriate Institutional Review Boards (IRBs) must approve the protocol, any amendments, and the subject informed consent form (ICF) prior to implementation.

Freely given written informed consent must be obtained from every subject prior to participation in this clinical trial. As part of this procedure, the Investigator must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the study subject is aware of the potential risks, inconveniences, or AEs that may occur. The study subject should be informed that he/she is free to withdraw from the study at any time. He/she will receive all information that is required by federal regulations and ICH guidelines. The Investigator or designee will provide the Sponsor with a copy of the IRB-approved informed consent form prior to the start of the study. The rights, safety, and well-being of participating subjects are the most important considerations and should prevail over interests of science and society.

Study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). This trial will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of 5 once-weekly IV infusions of SYNT001 at different dose levels in subjects with chronic pemphigus (vulgaris or foliaceus).

3.2 Secondary Objectives

The secondary objectives of this study are as follow:

- To determine the PK of SYNT001 following 5 once-weekly 1-hour IV infusions at different dose levels
- To assess the effect of 5 once-weekly doses of SYNT001 at different dose levels on the following PD biomarkers:
 - o Immunoglobulins: IgG, IgG subtypes (IgG1-4), IgA, IgM
 - o Albumin
- To assess the effect of 5 once-weekly doses of SYNT001 at different dose levels on the following disease activity markers:
 - o Serum anti-desmoglein (Dsg) (1 and 3) antibody levels
 - o Pemphigus Disease Area Index (PDAI)
- To assess immunogenicity (anti-SYNT001 antibodies)

3.3 Exploratory Objectives

The exploratory objectives of this study are as follow:

- To assess the effect of 5 once-weekly doses of SYNT001 at different dose levels on the following biomarkers, including:
 - o Serum anti-epithelial cell antibody (AECA) levels by indirect immunofluorescence
 - o Circulating immune complexes (CIC)
 - o Complement component 3 (C3)
 - Exploratory biomarkers (FCGR2A single nucleotide polymorphism-SNP, RNAseq, urine IgG)
 - Immune phenotyping by flow cytometry for CD3⁺CD4⁺ T, CD3⁺CD8⁺ T, monocytes, NK cells and B cells
 - o SYNT001 levels in skin biopsies (optional)
- To characterize corticosteroid use during the study

4 STUDY DESIGN

4.1 Study Sites

This study will be conducted at approximately 10 sites in the United States (US).

4.2 Study Endpoints

Primary Outcome Measures: Assessment of safety data (adverse events [AEs], serious adverse events [SAEs], vital sign measurements, ECGs and clinical laboratory tests) will be the primary safety measure.

Secondary Outcome Measures

Pharmacokinetics:

Half-life (t_{1/2}), maximum plasma concentration determined directly from the concentration-time profile (C_{max}), observed time to reach peak plasma concentration (T_{max}), area under the plasma concentration-time curve from pre-dose (time 0) to 24 hours post-dose (AUC₀₋₂₄), and area under the plasma concentration-time curve from pre-dose (time 0) to infinity (AUC_{0-∞})

PD Biomarkers:

- Ig Assessments: Serial assessments of total IgG and IgG subtypes (IgG1-4)
 - o Serial assessments of total IgG and IgG subtypes (IgG1-4)
 - o IgA levels
 - o IgM levels
- Albumin levels

Disease activity markers:

- Serum anti-desmoglein (Dsg) (1 and 3) antibody levels
- Pemphigus Disease Area Index (PDAI) scores

Immunogenicity:

• Anti-SYNT001 antibodies

Exploratory Outcome Measures

Biomarkers, including:

- CIC
- C3
- Serum AECA levels
- Exploratory biomarkers (FCGR2A SNP, RNAseq, urine IgG)

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- Immune phenotyping by flow cytometry for measurement of CD3⁺CD4⁺ T, CD3⁺CD8⁺ T, monocytes, NK cells and B cells
- SYNT001 levels in skin biopsies (optional)

Concomitant Treatments

Corticosteroid use

Further details on the statistical and analytical plan for these endpoints are available in Section 12, Statistical Considerations.

4.3 Overview of Study Design

This will be a multicenter, open-label study to assess the safety, tolerability, activity, PK, PD, and immunogenicity of 5 once-weekly IV infusions of SYNT001 to subjects with chronic pemphigus (vulgaris or foliaceus).

Planned doses of SYNT001 to be studied are 10 mg/kg and up to 30 mg/kg. Two cohorts of 8 eligible subjects each will receive 5 once-weekly 60-minute infusions of SYNT001 10 mg/kg or up to 30 mg/kg. Based on review of safety, PD, and clinical outcomes of the first cohort, the dose for the second cohort may be adjusted, but with a maximum dose of 30 mg/kg. Based on review of safety, PD and clinical outcomes from these 2 cohorts, a third cohort of up to 8 subjects may be treated at another dose, with a maximum dose of 45 mg/kg, but may also be lower than 10 mg/kg or between 10 and 30 mg/kg, inclusive.

Cohort	No. of Subjects	Dose
1	8	SYNT001 10 mg/kg
2	8	SYNT001 30 mg/kg

Cohorts will be dosed sequentially beginning with Cohort 1. The first 2 subjects will be dosed at least 24 hours apart. A review of the 24-hour safety data for the first subject will be performed to ensure that there are no overt safety concerns before dosing the second subject. A review of the 7-day safety data for the first 2 subjects will be performed prior to dosing the remaining 6 subjects in the cohort. This evaluation will include a review of AE/SAE reports, vital sign assessments, physical examinations, ECGs and clinical laboratory testing. The seriousness, severity, and relatedness of AEs/SAEs will also be considered in the safety evaluation. Safety data will be reviewed on a continuous basis throughout the study. All data through Day 42

(2 weeks after the last subject's last dose in Cohort 1) will be reviewed before Cohort 2 is initiated. Cohort 2 and Cohort 3, if added, will be dosed per the same schedule.

Safety evaluations will be conducted by a dose escalation committee (DEC). The DEC will consist of the Medical Monitor, an Independent Clinical Expert and a Syntimmune Medical Officer. To assist in the safety assessments, the DEC may request that Investigators, other experts, or members within their organizations review the data and participate in the discussions. Dosing and dose escalation will proceed if the DEC has determined that it would be safe and appropriate to do so. In addition, over the course of the study, the DEC will review any drug-related SAEs to determine if modifications to the study or other measures are necessary to ensure the safety of the subjects.

On days where study drug is administered, vital sign and pulse oximetry measurements will be collected immediately prior to the infusion; 15, 30, and 45 minutes after the start of the infusion; at completion of the infusion; and 30 minutes, 1 hour and 2 hours following completion of the infusion.

On Days 0 and 28, PK blood samples will be collected prior to infusion start and then over the subsequent 48 hours. Subjects will remain at the clinic through the 6-hour PK sample collection and will return to the clinic for the 24- and 48-hour collections. Additional samples will be collected on Days 5 and 33.

On Day 0 photographs will be taken of active lesions. Follow-up photographs will be taken of the same areas on Days 33 and 56. If a subject begins a steroid taper, additional photographs will be taken at the clinic visit during which the decision to begin the taper is made.

Subsequent visits will occur on Days 1, 2, 5, 7, 12, 14, 19, 21, 28, 29, 30, 33, and 42 for safety assessments, study drug dosing, sample collections, and other study procedures.

Subjects also will return to the clinic on Day 56 (28 days after receiving their last dose of study drug) for an End-of-Study/Follow-Up visit.

See Table 1 for a schedule of all study events. To assess safety and tolerability, subjects will undergo physical examinations (PEs; including weight), vital sign measurements, clinical (safety) laboratory tests, AE assessments, concomitant medication assessments, and electrocardiograms (ECG).

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Note: No vaccinations may be given from within 2 weeks of screening until 2 months following the last dose of study drug.

4.4 Randomization and Blinding

This is an open-label study.

5 STUDY POPULATION

5.1 Target Population

This study will be conducted in approximately 16 male and female subjects (2 cohorts of 8 subjects each) with a confirmed diagnosis of pemphigus (vulgaris or foliaceus); however, a third cohort of up to 8 subjects may be added. Subjects will be enrolled only once in the study and will not be included in subsequent dosing cohorts. Subjects who withdraw for any reason other than an AE and who do not receive study drug or have only received one dose of study drug may be replaced, up to one subject per cohort. Subjects who do not receive all doses of study drug will continue to be followed through 28 days after their last dose. The maximum number of subjects who may be enrolled in this study is 27 (24 + up to 3 replacements, as necessary). Within each dosing cohort, no more than 3 subjects may be enrolled with pemphigus foliaceus.

5.2 Inclusion Criteria

A subject must meet the following criteria to be eligible for the study:

- 1. Willing and able to read, understand and sign an informed consent form;
- 2. Male or female \geq 18 years of age;
- 3. Documented diagnosis of pemphigus vulgaris or foliaceus based on all 3 of the following criteria:
 - a. Documented clinical history consistent with pemphigus vulgaris or foliaceus (clinical presentation defined as mucosal and/ or skin lesions);
 - b. Presence of Anti-Dsg 1 or 3 antibodies above the upper limit of normal;
 - c. History of at least one positive tissue based test (biopsy, DIF)
- 4. Active disease: Lesions lasting > 2 weeks, and 3 active lesions in skin or mucosa or 2 active lesions with at least one being a skin lesion > 1 cm diameter:
 - a. If treated with rituximab or other anti-CD20 antibodies, last dose > 12 months prior to screening;
 - b. If being treated with other immunosuppressants (i.e., azathioprine, mycophenolate mofetil or cyclosporine), must be on stable dose (< 10% change in dose) for 6 weeks prior to screening;
 - c. If being treated with corticosteroids, must be ≤ 1mg/kg/day and stable (< 10% change in dose) for 2 weeks prior to screening;

- d. Allowed topical therapies for pemphigus lesions upon entering the study include petroleum jelly or Aquaphor® for the skin or chlorhexidine for the mouth
- 5. Body mass index (BMI) $18.5 35.0 \text{ kg/m}^2$;
- 6. Has a negative urine pregnancy test (for women of childbearing potential) documented prior to the first dose of study drug;
- 7. Females of childbearing potential must agree to be abstinent or else use any two of the following medically acceptable forms of contraception (<1% per year failure rate) from the Screening Period through 60 days after the final study dose: oral contraceptive, condom with or without spermicidal jelly, diaphragm or cervical cap with spermicidal jelly, or intra-uterine device (IUD). A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception.
- 8. Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months do not require contraception during the study.
- 9. Males with female partners of childbearing potential, including males who are surgically sterile (post vasectomy), must agree to be abstinent or else use a medically acceptable form of contraception from the screening period through 60 days after the final study dose.

5.3 Exclusion Criteria

A subject who meets any of the following criteria is ineligible for the study:

- 1. Unable or unwilling to comply with the protocol;
- Active non-hematologic malignancy or history of non-hematologic malignancy in the 3 years prior to screening (exclusive of non-melanoma skin cancer and cervical cancer in situ);
- 3. Positive for HIV or hepatitis C antibody;
- 4. Positive for hepatitis B surface antigen;
- 5. Active infection or history of recurrent infections;
- 6. IVIG treatment within 60 days of screening;

- 7. Received any cytotoxic (other than azathioprine) or mAb therapy in the 3 months prior to screening;
- 8. Any exposure to an investigational drug or device within 30 days prior to screening;
- 9. Plasmapheresis or immunoadsorption within 60 days of screening
- 10. Cellular therapy at any time prior to screening
- 11. Use of any immunosuppressive drugs apart from corticosteroids, azathioprine, mycophenolate mofetil, or cyclosporine within 3 months of screening;
- 12. Serum total IgG < 600 mg/dL;
- 13. Subject has any current medical condition that, in the opinion of the Investigator, may compromise their safety or compliance, preclude successful conduct of the study, or interfere with interpretation of the results (e.g., a significant pre-existing illness or other major comorbidity that the Investigator considers may confound the interpretation of the study results);
- 14. Any vaccination within 2 weeks of screening

6 STUDY PROCEDURES

6.1 Informed Consent

All subjects must take part in the informed consent process. Adequate time must be allowed for the subject to ask questions and make a voluntary decision. No protocol-specific procedures, including screening procedures, are to be performed until the subject has signed and dated an IRB-approved ICF. Subjects may withdraw consent at any time. Participation in the study may be terminated at any time without the subject's consent as determined by the Investigator.

6.2 Demographics and Medical History

Demographics (age, gender, race and ethnicity) and medical history will be obtained from the subject and recorded on the source document and eCRF. Medical history will capture the subject's current medical history (current disease processes), past medical status (past disease processes), history of surgery and concomitant treatments.

6.3 Physical Examination

A complete physical examination will be performed as outlined in Table 1. The complete PE will include measurements of weight (in kg) and height (in cm; height to be measured only at screening visit) and a review of the following body systems:

- General appearance
- Head, eyes, ears, nose, and throat
- Neck
- Respiratory
- Cardiovascular
- Abdomen
- Neurologic
- Extremities
- Dermatologic
- Lymphatic

Any abnormal and clinically significant findings from the PE must be recorded in the appropriate eCRF. Findings at screening and Day 0 (pre-dose) will be recorded as medical history.

6.4 Pemphigus Disease Area Index (PDAI) Scoring

Pemphigus severity and disease activity will be measured using the PDAI. See Appendix B.

6.5 Vital Sign Measurements

Vital sign measurements will be collected after the subject has been sitting for 5 minutes. Vital sign assessments will include measurements of sitting blood pressure (mm Hg), heart rate (beats

per minute), respiration rate (breaths per minute), oral temperature (Celsius). Abnormal results are to be repeated after 5 minutes of rest. Pulse oximetry (%) also is to be measured. See Table 2 for timing window allowances with respect to measurement collection.

On Days 0, 7, 14, 21, and 28, vital sign measurements are to be obtained immediately prior to the infusion; 15, 30, and 45 minutes after the start of the infusion; at completion of the infusion; and 30 minutes, 1 hour and 2 hours following completion of the infusion. Details on the management of mild to moderate and severe infusion reactions can be found in Figure 1 and Figure 2. Abnormalities in vital sign measurements will be graded in severity per the NCI CTCAE scale Version 4.03.

Subjects should be seated quietly for at least 5 minutes in a chair with their backs supported, their feet flat on floor (legs uncrossed), and their arms bared on a hard surface, with the arm slightly abducted and bent, with palm up and the midpoint of upper arm at heart level. Correct cuff and bladder size should be utilized and the same cuff and arm should be used per subject throughout study.

6.6 12-Lead Electrocardiogram (ECG)

Digital 12-lead ECG measurements will be obtained at screening, on Days 0 and 28 at 5 minutes after the completion of the infusion and at the Day 56 (Follow-Up) Visit. Subjects who conduct their Day 12 visit at the investigative site, as opposed to an at-home nurse visit, will have an additional ECG performed. ECGs are to be performed with the subject in a supine position having rested in this position for at least 5 minutes before each reading. ECGs are to be performed in triplicate, each 1 to 2 minutes apart. See Table 2 for timing window allowances with respect to performing ECG.

The following ECG parameters will be collected: PR interval, RR interval, QRS interval, and QT interval. The ECG findings will be evaluated by a qualified physician for the presence of abnormalities (qualitative assessment). The physician will assess each ECG as normal, abnormal/not clinically significant, or abnormal/clinically significant.

Normal QTcF is ≤ 450 msec.

Abnormalities in the ECG that appear following therapy or that result in clinical signs and symptoms are considered clinically significant for the purposes of this study and will be recorded on the AE eCRF.

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6.7 Clinical Laboratory Measurements

Collection time for all safety, PD, and exploratory labs are outlined in Table 1.

Laboratory testing (hematology, urinalysis, serum chemistry, virology, serology, pregnancy tests, PD samples, PK samples, and anti-drug antibody samples) will be performed using established methods by a central laboratory. Safety laboratory panels are defined as listed in Table 3. Blood and urine samples for hematology, serum chemistry, and urinalysis will be prepared using standard procedures. Results will be provided to the Investigator. Aliquots from the PK, biomarker and anti-drug antibody samples may be retained as back-up for additional testing as necessary. Subjects will be in a seated or supine position during blood collection. Full clinical safety lab draws will be collected at Screening and on Days 0, 7, 14, 21, 28, 33, 42 and 56. The total blood draw for each subject who completes the study at Day 56, will be approximately 308 mL. Please refer to the Laboratory Manual for more information.

Table 3: Clinical Laboratory Panels

Hematology	Serum Chemistry	Urinalysis
CBC with differential Erythrocyte Sedimentation Rate (ESR)	 Albumin Alkaline phosphatase ALT AST BUN Calcium Carbon dioxide Chloride Creatinine Glucose LDH Phosphorus Potassium Sodium Total and direct bilirubin Total protein Uric acid C-Reactive Protein 	 Appearance Color pH Specific gravity Ketones Protein Glucose Nitrite Urobilinogen Blood/hemoglobin Leukocyte esterase Bilirubin Microscopic examination of sediment: only if the results of the urinalysis dipstick evaluation are positive for blood/hemoglobin
Virology • Hepatitis C		
Hepatitis B		

- HIV
- VZV
- Tetanus

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count; BUN = blood urea nitrogen; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; VZV = varicella-zoster virus

Abnormalities in clinical laboratory tests that are considered clinically significant are to be recorded on the AE electronic case report form (eCRF) page. Laboratory results will be graded using the NCI CTCAE, Version 4.03. If laboratory values constitute part of an event that meets criteria defining it as serious, the event (and associated laboratory values) must be reported as an SAE (see Section 11.3.1).

6.7.1 Pregnancy Testing

Pregnancy testing will be performed for women of childbearing potential at screening and prior to first dose of SYNT001 on Day 0 and Day 56 (urine or serum test is acceptable however, positive urine tests must be confirmed with serum testing.)

6.7.2 Virology

Testing for HCV antibody, hepatitis B surface antigen, and HIV antibody will be performed at screening.

6.7.3 Serum Tetanus Antibody and Varicella-Zoster Virus Antibody Testing

Samples for serum tetanus antibody and varicella-zoster virus antibody testing are to be collected at baseline (pre-dose, Day 0) and on Day 56 (Follow-Up visit). Testing at Day 56 will not be done for any subject whose baseline titer is below the level of detection. Specifically, if the baseline VZV titer is above the detectable level, but tetanus is not, only the VZV antibody titer will be tested on Day 56. If the Day 56 results are below the baseline value, defined as greater than 30% below the baseline value, or if the subject falls below the level of detection, the subject will be re-tested at 1 month after the Follow-Up visit (approximately 2 months after the subject's last dose); if still below the baseline value (or level of detection), the subject will be re-tested after another month (3 months after last dose). Any subject whose baseline value for tetanus or VZV was above the detectable level at baseline, and is not within 30% of the baseline value or is below the detectable level on Day 56 and upon 2 retests (2 and 3 months following last dose of SYNT001), will be referred to their primary care physician for further management.

6.7.4 Pharmacokinetics (PK) Sampling

Starting on Days 0 and 28, serum samples will be collected just prior to the start of study drug infusion (pre-dose), at 5 minutes and 2, 4, 6, 24, and 48 hours after the end-of-study drug infusion. Additional samples will be collected on Days 5 and 33. The actual time and date of each blood draw is to be recorded.

Study drug concentration will be used to calculate the following PK parameters: $t_{1/2}$, C_{max} , T_{max} , AUC_{0-24} , and $AUC_{0-\infty}$.

Detailed instructions for sample collection and preparation will be provided in a separate laboratory manual

6.7.5 Pharmacodynamic Sampling

PD samples will be collected for analyses throughout the study. On Days 0, 7, 14, 21, and 28, samples should be collected prior to infusion of study drug. Measurements for albumin PD biomarkers will be derived from the clinical safety laboratory results. Samples for each type of PD will be collected according to the schedule shown in Table 4.

Table 4: Pharmacodynamic/ Activity Assessments

Parameter	Collection Timepoints		
IgG, IgG subtypes (IgG1-4), IgA, IgM	Screening, and Days 0, 1, 2, 5, 7, 12, 14, 19, 21, 28, 29, 30, 33, 42, and 56		
Circulating immune complexes (CIC)	Days 0, 5, 7, 12, 14, 19, 21, 28, 33, 42, and 56		
• Albumin	Screening, and Days 0, 7, 14,21, 28, 33, 42, and 56		
Anti-Dsg (1 and 3) antibody titer	Screening, Days 0, 7, 14, 33, and 56		
 Complement component 3 (C3) Anti-epithelial cell antibody (AECA) levels by indirect immunofluorescence 	Days 0, 14, 33, and 56		
Exploratory biomarker (RNAseq, Urine IgG)	Days 0, 14, 33, and 56		
Immune phenotyping by flow cytometry for measurement of CD3 ⁺ CD4 ⁺ T, CD3 ⁺ CD8 ⁺ T, monocytes, NK cells and B cells	Days 0 and 28		
Exploratory biomarker (FCGR2A SNP)	Day 0		

See Table 2 for timing window allowances with respect to measurement collection. Detailed instructions for sample collection (including collection tubes) and preparation will be provided in a separate laboratory manual.

6.7.6 Immunogenicity Testing

Up to 4 serum samples will be collected for immunogenicity analyses. Samples will be collected on Days 0 (pre-dose), 14, 28, and 56.

SYNT001 is being developed for the acute and chronic therapy of autoimmune disorders. Although SYNT001 is a humanized IgG4 monoclonal antibody, exposure to SYNT001 in clinical trials could result in the development of anti-drug antibodies (ADAs), with potential consequences ranging from neutralization or lessening of drug efficacy to safety consequences such as allergic reactions. Testing will first detect binding ADAs, then, for all confirmed positive samples, there will be testing for neutralizing effects.

Detailed instructions for sample collection and preparation will be provided in a separate laboratory manual.

6.8 Study Drug Administration

Two cohorts of 8 eligible subjects each will receive 5 once-weekly 60-minute IV infusions of SYNT001 10 mg/kg or up to 30 mg/kg. SYNT001 will be given as a 250-mL IV infusion over 1 hour using a 0.2-micron, inline filter. Based on review of safety data, as well as available and relevant PD results, and clinical outcomes of Cohort 1, a decision about proceeding with Cohort 2 will be made. Based on review of all safety data, available PD results, and clinical outcomes of these 2 cohorts, a third cohort of 8 subjects may be treated at another dose, with a maximum dose of 45 mg/kg, but may also be lower than 10 mg/kg or between 10 and 30 mg/kg, inclusive.

Cohort No.	Study Drug	Dose Level (mg/kg/dose)
1	SYNT001	10 mg/kg
2	SYNT001	30 mg/kg

See Section 9.1 for dosing schedule.

6.9 Prior and Concomitant Medications

All medications a subject receives within 14 days prior to enrollment through the end of the study (Day 56) will be documented on the source document and eCRF.

Note: No vaccinations may be given from within 2 weeks of screening until 2 months following the last dose of study drug.

6.10 Adverse Event Assessments

Information regarding the occurrence of AEs will be collected from the time the subject signs the informed consent form throughout their participation in the study, including a period of 28 days after study drug dosing. Findings at screening and Day 0 (pre-dose) will be recorded as medical history. Any known untoward event that occurs beyond the AE reporting period that the Investigator assesses as related to study drug also should be reported as an AE.

Clinical AEs will be graded using the NCI CTCAE, Version 4.03 (Appendix A).

Note: AEs resulting in a subject's permanent discontinuation from the study, regardless of seriousness or relationship to study drug, MUST be promptly reported to the sponsor. Additionally, subjects must be followed until return to normal and/or resolution of the AE.

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See Section 11 for more information.

6.11 Photographs

On Day 0 photographs will be taken of active lesions. Follow-up photographs will be taken of the same areas on Days 33 and 56. Subjects who begin a steroid taper will have additional photographs taken at the clinic visit during which the decision to begin the taper is made. A separate manual describing the procedures for taking photographs will be provided.

6.12 Skin Biopsy

Optional skin biopsy samples will be collected on Day 0 pre-dose and on Days 1, 2, 14, 33 and 56 to analyze SYNT001 levels.

7 STUDY ASSESSMENTS

7.1 Screening Period: Day -14 to Day -1

Informed consent must be obtained before any study-specific samples are taken or study-specific tests or evaluations are conducted. The following assessments at the screening visit are to occur within 14 days before dosing. Study eligibility will be based on satisfying all the study inclusion and exclusion criteria.

At the screening visit, information will be collected and subjects will have clinical evaluations as follows:

- Informed consent (Section 6.1)
- Medical history and demographic data (Section 6.2)
- Review inclusion and exclusion criteria (Section 5.2, Section 5.3)
- Complete PE, including height and weight (Section 6.3)
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- 12-Lead ECG (to be obtained in triplicate after 5 minutes of rest in the supine position) (Section 6.6)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- Pregnancy test (Section 6.7)
- Hepatitis and HIV screen (Section 6.7)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - Anti-Dsg (1 and 3) antibody titer
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.2 Enrollment and First Treatment: Day 0

Study Day 0 is defined as the date the subject is administered their first dose of study drug. On Day 0, subjects will be asked to come to the clinic and the following procedures will be performed prior to the first dose of study drug:

- Complete physical exam (Section 6.3)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature); to be measured immediately prior to the infusion (Section 6.5)
- Pulse oximetry (to be measured immediately prior to the infusion) (Section 6.5)

- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- Pregnancy test (Section 6.7)
- Serum tetanus antibody and VZV antibody (Section 6.7)
- PDAI Score (Section 6.4)
- PK baseline sample collection (collected just prior to the start of the study drug infusion) (Section 6.7)
- Immunogenicity sample collection (collected just prior to the start of study drug infusion) (Section 6.7)
- PD sample collection (collected just prior to the start of the study drug infusion) (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - Anti-Dsg (1 and 3) antibody titer
 - CIC
 - C3
 - AECA
 - FCGR2A SNP
 - RNAseq
 - Urine IgG
 - Immune phenotyping
- Optional skin biopsy (Section 6.12)
- Photography (Section 6.11)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After the preceding procedures and assessments are completed:

- Study drug administration (record date and time of dose of study drug) (Section 9)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) will be performed at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion (Section 6.5)
- Pulse oximetry will be measured at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion (Section 6.5)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After administration of study drug, the following post treatment procedures and assessments will be performed:

• Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral

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temperature): 30 minutes, 1 hour and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest (Section 6.5)

- Pulse oximetry: 30 minutes, 1 hour and 2 hours following completion of the infusion (Section 6.5)
- PK sample collection at 5 minutes and 2, 4, 6 hours after the end-of-study drug infusion; record collection date and time for each PK sample (Section 6.7)
- 12-Lead ECG (to be obtained in triplicate at 5 minutes after the completion of study drug infusion (Section 6.6)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.3 Follow-up: Day 1

On Day 1 (24 hours \pm 1 hour from end-of-infusion time on Day 0), the subject will return to the clinic and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
- PK sampling (record collection date and time) (Section 6.7)
- Optional skin biopsy (Section 6.12)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.4 Follow-up: Day 2

On Day 2 (48 hours \pm 2 hours from end-of-infusion time on Day 0), the subject will return to the clinic and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
- PK sampling (record collection date and time) (Section 6.7)
- Optional skin biopsy (Section 6.12)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.5 Follow-up: Day 5

On Day 5 (120 hours \pm 4 hours from end-of-infusion time on Day 0), subjects may return to the clinic or be visited by at-home nurse, and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- PK sampling (record collection date and time) (Section 6.7)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.6 Treatment Day 7 (Dose 2)

On Day 7 (\pm 6 hours) subjects will return to the clinic and the following procedures are to be performed prior to study drug infusion:

- Complete physical exam (Section 6.3)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature); to be measured immediately prior to the infusion (Section 6.5)
- Pulse oximetry (to be measured immediately prior to the infusion) (Section 6.5)
- PDAI Score (Section 6.4)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- PD sample collection (collected just prior to the start of the study drug infusion) (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titer
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After the preceding procedures and assessments are completed:

- Study drug administration (record date and time of dose of study drug) (Section 9)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) will be performed at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion (Section 6.5)
- Pulse oximetry will be measured at 15, 30, and 45 minutes after the start of the infusion

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and at completion of the infusion (Section 6.5)

- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After administration of study drug, the following post treatment procedures and assessments will be performed:

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature): 30 minutes, 1 hour and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Pulse oximetry: 30 minutes, 1 hour and 2 hours following completion of the infusion (Section 6.5)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.7 Dose 2 Follow-up Day 12

On Day 12 (\pm 6 hours) the subject may will return to the clinic, or be visited by at-home nurse, and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
- If visit performed at the study site: 12-Lead ECG to be obtained in triplicate (Section 6.6)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.8 Treatment Day 14 (Dose 3)

On Day 14 (\pm 6 hours) subjects will return to the clinic and the following procedures are to be performed prior to study drug infusion:

- Complete physical exam (Section 6.3)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature); to be measured immediately prior to the infusion (Section 6.5)
- Pulse oximetry (to be measured immediately prior to the infusion) (Section 6.5)
- PDAI Score (Section 6.4)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)

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- Immunogenicity sample collection (collected just prior to the start of study drug infusion) (Section 6.7)
- PD sample collection (collected just prior to the start of the study drug infusion) (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - Anti-Dsg (1 and 3) antibody titer
 - CIC
 - C3
 - AECA
 - RNAseq
 - Urine IgG
- Optional skin biopsy (Section 6.12)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After the preceding procedures and assessments are completed:

- Study drug administration (record date and time of dose of study drug) (Section 9)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) will be performed at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion (Section 6.5)
- Pulse oximetry will be measured at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion (Section 6.5)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After administration of study drug, the following post treatment procedures and assessments will be performed:

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature): 30 minutes, 1 hour and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Pulse oximetry: 30 minutes, 1 hour and 2 hours following completion of the infusion (Section 6.5)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.9 Dose 3 Follow-up Day 19

On Day 19 (\pm 6 hours) the subject may return to the clinic, or be visited by an at-home nurse, and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.10 Treatment Day 21 (Dose 4)

On Day 21, $(\pm 6 \text{ hours})$ subjects will return to the clinic and the following procedures are to be performed prior to study drug infusion:

- Complete physical exam (Section 6.3)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature); to be measured immediately prior to the infusion (Section 6.5)
- Pulse oximetry (to be measured immediately prior to the infusion) (Section 6.5)
- PDAI Score (Section 6.4)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- PD sample collection (collected just prior to the start of the study drug infusion) (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After the preceding procedures and assessments are completed:

- Study drug administration (record date and time of dose of study drug) (Section 9)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) will be performed at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion (Section 6.5)
- Pulse oximetry will be measured at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion (Section 6.5)
- Concomitant medication assessment (Section 6.9)

• AE assessment (Section 6.10)

After administration of study drug, the following post treatment procedures and assessments will be performed:

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature): 30 minutes, 1 hour and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Pulse oximetry: 30 minutes, 1 hour and 2 hours following completion of the infusion (Section 6.5)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.11 Treatment Day 28 (Dose 5)

On Day 28 (\pm 1 Day), subjects will return to the clinic and the following procedures are to be performed prior to study drug infusion:

- Complete physical exam (Section 6.3)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature); to be measured immediately prior to the infusion (Section 6.5)
- Pulse oximetry (to be measured immediately prior to the infusion) (Section 6.5)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- PDAI Score (Section 6.4)
- PK sampling (collected just prior to the start of the study drug infusion; record collection date and time for each PK sample) (Section 6.7)
- Immunogenicity sample collection (collected just prior to the start of study drug infusion) (Section 6.7)
- PD sample collection (collected just prior to the start of the study drug infusion) (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Immune phenotyping
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After the preceding procedures and assessments are completed:

- Study drug administration (record date and time of dose of study drug) (Section 9)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) will be performed at 15, 30, and 45 minutes after the start of the infusion

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- and at completion of the infusion (Section 6.5)
- Pulse oximetry will be measured at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion (Section 6.5)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After administration of study drug, the following post treatment procedures and assessments will be performed:

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature): 30 minutes, 1 hour and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Pulse oximetry: 30 minutes, 1 hour and 2 hours following completion of the infusion (Section 6.5)
- PK sample collection at 5 minutes and 2, 4, 6 hours after the end-of-study drug infusion; record collection date and time for each PK sample (Section 6.7)
- 12-Lead ECG (to be obtained in triplicate at 5 minutes after the completion of study drug infusion (Section 6.6)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.12 Follow-up Day 29

On Day 29 (24 hours \pm 1 hour from end-of-infusion time on Day 28), the subject will return to the clinic and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
- PK sampling (record collection date and time) (Section 6.7)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.13 Follow-up Day 30

On Day 30 (48 hours \pm 2 hours from end-of-infusion time on Day 28), the subject will return to the clinic and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
- PK sampling (record collection date and time) (Section 6.7)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.14 Follow-up Day 33

On Day 33 (120 hours \pm 4 hours from end-of-infusion time on Day 28), subjects will return to the clinic and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- PDAI Score (Section 6.4)
- PK sampling (record collection date and time) (Section 6.7)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titer
 - C3
 - AECA
 - RNAseq
 - Urine IgG
- Optional skin biopsy (Section 6.12)
- Photography (Section 6.11)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.15 Follow-up Day 42

On Day 42 (\pm 3 days), subjects will return to the clinic and the following procedures are to be performed:

- Complete physical exam (Section 6.3)
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.16 Follow-up Day 56 (End-of-Study) or Early Termination Visit

On Day 56 (\pm 5 days), subjects are to return to the clinic and the following procedures are to be performed:

- Complete physical exam (Section 6.3)
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- Pregnancy test (Section 6.7)
- 12-Lead ECG (to be obtained in triplicate after 5 minutes of rest in the sitting position) (Section 6.5)
- Serum tetanus antibody and VZV antibody; Testing at Day 56 will not be done for any subject whose baseline titer is below the level of detection. See Section 6.7.3 for additional information.
- Immunogenicity sample collection (Section 6.7)
- PDAI Score (Section 6.4)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titer
 - C3

- AECA
- RNAseq
- Urine IgG
- Optional skin biopsy (Section 6.12)
- Photography (Section 6.11)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.17 Extended Follow-up Visits

Extended follow-up visits will occur only if additional testing for anti-tetanus and/ or anti-VZV titers are required. These visits will occur as needed at approximately 2 months post last dose and 3 months post last dose. See Section 6.7.3.

8 REMOVING SUBJECTS FROM STUDY

Every reasonable effort will be made to keep the subject in the study; however, if a subject is withdrawn from the study, every effort will be made by the Investigator to complete and report the reasons for withdrawal as thoroughly as possible. The reason(s) for termination must be clearly documented on the appropriate page of the eCRF. Once a subject discontinues from the study for any reason, every effort will be made to collect all clinical and laboratory data as scheduled for the Early Termination Visit (See Table 1). A termination eCRF must be completed for all enrolled subjects.

8.1 Subject Withdrawal

A subject's participation in the study may be prematurely discontinued for any of the following reasons:

- 1. The subject wishes to withdraw from the study.
- 2. Request by a regulatory agency (e.g., Institutional Review Board).
- 3. Subject experiences a significant or intolerable AE.
- 4. The subject experiences a significant adverse change in vital signs, PE findings, or a clinical laboratory parameter.
- 5. The subject has a need for a concomitant medication that is not permitted by the study protocol.
- 6. The subject experiences generalized impairment or mental incompetence that would result in the subject being unable to understand his or her participation in the study.
- 7. If, in the Investigator's medical judgment, further participation would be injurious to the health and well-being of the subject, or is not in the best interest of the subject.
- 8. Administrative reasons, such as subject non-compliance or a major protocol violation.

Subjects who are withdrawn from this study due to an AE determined to be related to study drug are to be followed until there is either:

- Resolution or stabilization of the AE determined to be related
- The subject is lost to follow-up
- The event is otherwise explained

If there is a persistent AE contributing to discontinuation that is determined to be related to SYNT001, subjects must be followed with appropriate medical management until resolution or stabilization.

A reasonable effort should be made to contact any subject lost to follow-up during the study to complete assessments and retrieve any outstanding data. If the subjects are unreachable by telephone after three (3) attempts, the minimum of a registered letter should be sent requesting that contact be made with the Investigator to report survival information.

8.2 Study Discontinuation

Syntimmune Inc. has the right to terminate or to stop the study at any time. Reasons for study discontinuation may include, but are not limited to the following:

- The incidence or severity of AEs in this or other related studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory
- Drug supply issues
- Excessive subject self-withdrawal
- Significant protocol violations (e.g., violation of eligibility criteria, dosing errors, missing data for study endpoint analysis)

8.3 Replacements

Enrolled subjects withdrawn for a reason other than an AE will be replaced if they have not been dosed or have only received one dose of study drug at the time of discontinuation, up to one subject per cohort. Subjects who do not receive all doses of study drug will continue to be followed through 28 days after their last dose.

8.4 Stopping Rule

8.4.1 Dose-Escalation Stopping Rule

Dose-limiting toxicity (DLT) will be defined generally as clinically significant, severe (Grade 3) AEs occurring in \geq 2 subjects that are determined to be clinically significant and considered related to study drug.

If 2 or more subjects at any time in any cohort (8 total subjects per cohort) have Grade 3 AEs that are determined to be clinically significant and considered to be related to study drug, dosing will be halted within that cohort and no further dose-escalation will occur. If the dose-escalation

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stopping rule is met in Cohort 1 (10 mg/kg) all safety data and all available pharmacodynamics will be reviewed and a cohort may be added at a dose at least 50% lower than the 10 mg/kg dose. If the stopping rule is not met after Cohort 1, dose-escalation may proceed up to a maximum of 30 mg/kg. If the dose-escalation stopping rule is met in Cohort 2, all safety data and all available pharmacodynamics will be reviewed and a cohort may be added at a dose a minimum of 30% lower than the Cohort 2 dose. If the stopping rule is not met after Cohort 2, dose-escalation may proceed up to a maximum of 45 mg/kg; however, this cohort may also receive a dose equal to or less than 30 mg/kg based on evaluation of all safety and pharmacodynamic data.

8.4.2 Study Stopping Rule

If any subject experiences a life-threatening AE (Grade 4) that is considered to be related to study drug, further dosing in all enrolled subjects will be suspended until the DEC has evaluated the event and determined the appropriate course of action. At any time during the study, the study may be discontinued if the DEC determines that further drug exposure would pose an undue risk to subjects.

8.4.3 Individual Stopping Rule

Dosing for any individual subject will be discontinued (i.e., no further study drug will be given to that subject) if the subject experiences any study drug-related SAE or any study drug-related non-SAE adverse event that, in the judgement of the Investigator and Medical Monitor suggest that it could be unsafe to administer further study drug to that subject. Additionally, a subject may be discontinued from further treatment with study drug, at the discretion of the Investigator with consultation with the Medical Monitor, if they require a significant increase in dose(s) of anti-pemphigus medication(s) for the management of pemphigus.

9 STUDY DRUG

For detailed information regarding SYNT001 preparation and administration, refer to the Pharmacy Manual.

9.1 SYNT001

SYNT001 is provided in vials containing 5 mL SYNT001 (extractable volume) at a nominal concentration of 50 mg/mL. The product is supplied as a liquid at pH 6.5 ± 0.5 . SYNT001 is diluted in Dextrose 5% in Water (D5W) to prepare the solution for infusion. SYNT001 will be infused via IV in 250 mL over 1 hour using a 0.2-micron, inline filter.

Two cohorts of 8 eligible subjects each will receive 5 once-weekly 60-minute infusions of SYNT001 in planned doses of 10 mg/kg or 30 mg/kg. Based on review of safety, PD, and clinical outcomes of these two cohorts, a third cohort of up to 8 subjects may be treated at another dose, with a maximum dose of 45 mg/kg, but may also be lower than 10 mg/kg or between 10 and 30 mg/kg, inclusive.

The specification for host cell DNA in SYNT001 is < 2 pg/mg, the limit of quantitation of the assay. To comply with regulatory guidelines, which specify a maximum level of 10 ng host cell DNA per dose, dosing is limited to 5000 mg of SYNT001. Therefore, at the highest dose possible in this study (45 mg/kg), maximum subject weight will be limited to 111 kg.

9.2 Cohort Dosing

Cohorts will be dosed sequentially beginning with Cohort 1. The first 2 subjects will be dosed at least 24 hours apart. A review of the 24-hour safety data for the first subject will be performed to ensure that there are no overt safety concerns before dosing the second subject. A review of the 7-day safety data for the first 2 subjects will be performed prior to dosing the remaining 6 subjects in the cohort. Cohort 2, and Cohort 3 if added, will be dosed per the same schedule

9.3 Timing of Dosing

On Days 0, 7, 14, 21, and 28, subjects will receive a 60-minute IV infusion of SYNT001 in the morning. The date and time the dose is administered will be recorded.

9.4 Identity of Investigational Products

All supplies of SYNT001 will be supplied by Syntimmune and must be stored refrigerated (2°C to 8°C/36°F to 46°F) in the carton and protected from light, in a securely locked area, accessible to authorized persons only, until needed for dose preparation. Qualified site personnel will

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inventory the investigational product received and will maintain records of disposition of the drug, including dates, quantity and use.

9.5 Investigational Product Retention at Study Site

The Investigator (or designee) is responsible for maintaining accurate accountability records of the investigational product throughout the clinical study. All study drug received at the site must be inventoried and accounted for in an accountability log provided by the Sponsor. All dispensing and accountability records will be available for Sponsor review. Study drug accountability will be verified during on-site monitoring visits.

Upon the completion or termination of the study, and upon written authorization from the Sponsor, or its representative, all unused and/or partially used study drug should be returned or destroyed at the investigational site, as specified by Sponsor. It is the Investigator's responsibility to ensure that the Sponsor, or its representative, has provided written authorization that procedures for proper disposal of the study drug have been established, and that appropriate records of the disposal are documented and maintained. No unused study drug may be disposed until fully accounted for by the Sponsor monitor (or designee)

9.6 Warnings and Precautions

Note: Subjects must not receive any vaccinations from within 2 weeks of screening until 2 months after the last dose of study drug.

9.6.1 Infusion Reaction

SYNT001 will be given as an IV infusion over 1 hour. As with all mAbs administered by IV infusion, infusion reactions are possible. In nonclinical testing of SYNT001 in NHPs, clinical observations were limited to infusion reactions due to the immunogenicity of SYNT001 in NHPs. These reactions included transient emesis/vomitus which typically occurred within 1 hour of dosing at all dose groups, but only after the third weekly infusion following the development of ADAs. Transient histamine-type responses were noted 30 minutes post-dose in some animals in all dose groups, but only following the third weekly infusion as above. These reactions were consistent with a histamine reaction (decreased activity, periocular swelling, erythema, facial flushing, eyelids partially/completely closed, and/or generalized weakness). With the exception of vomitus/emesis and red skin discoloration associated with injection or blood draw sites, these observations spontaneously resolved within 1-hour post-dose. Subsequent pretreatment with intramuscular diphenhydramine prevented further histamine-type reactions. All doses of SYNT001 were administered by bolus infusion over approximately 5 minutes in the NHP

studies. However, all of the observed infusion reactions (including vomitus/emesis and histamine-type reactions) associated with ADAs are not at all predictive of what may occur in humans [Bugelski 2004, Ponce 2009] and furthermore, are not considered relevant to predicting responses in humans [ICH S6(R1) 2011].

Typically, infusion reactions to monoclonal antibodies observed in human studies develop within 30 minutes to 2 hours after the initiation of drug infusion, although symptoms may be delayed for up to 24 hours. Most are mild in severity, although severe and even fatal reactions can occur.

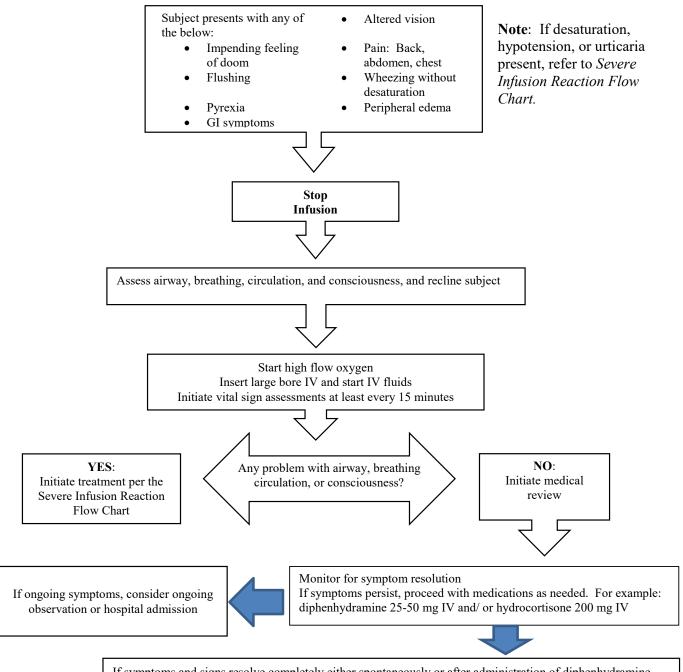
Guidelines for Grading and Management of Allergic or Infusion-Related Reactions

Allergic and/or infusion-related reactions include hypersensitivity reactions and cytokine release syndromes. These reactions are experienced by patients during or within hours of the infusion of monoclonal antibody therapy. Symptoms can include flushing, alterations in heart rate and blood pressure, dyspnea, bronchospasm, back pain, fever, urticaria, edema, nausea, and all types of rashes. Anaphylaxis is recognized as a severe, life-threatening, generalized, or systemic reaction. This is a medical emergency characterized by rapidly developing life-threatening airway and/or breathing and/or circulation problems usually associated with skin or mucosal changes.

Management of Grade 1 infusion reactions include decreasing the rate of infusion by 50% and observing. Symptoms may also be treated as needed with medications such as diphenhydramine, hydrocortisone or acetaminophen.

Management of Grade 2 and higher infusion reactions should include stopping the infusion of study drug. See Figure 1 and Figure 2 for details on the management of Grades 1-2 and Grade 3 or higher infusion reactions. The severity of and management of allergic or infusion-related reactions will be graded and managed using NCI CTCAE Version 4.03 (see Table 5).

Figure 1: Management of Mild (Grade 1) to Moderate (Grade 2) Infusion Reactions



If symptoms and signs resolve completely either spontaneously or after administration of diphenhydramine with or without hydrocortisone, consider rechallenge:

Wait at least 20 minutes following medication administration before commencing rechallenge at an infusion rate of 50% or less of the initial infusion rate or

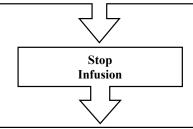
Consider pre-medicating the subject with the same medication(s) 20-30 minutes in advance of subsequent administrations of SYNT001 and starting infusion at 50% of the planned infusion rate for the first 30 minutes, then returning to the intended infusion rate in the absence of any infusion reaction

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Figure 2: Management of Severe (Grade 3 or higher) Infusion Reactions

Subject presents with any of the below:

- Urticaria
- Airway threatened by angioedema
- Angioedema: Lip, mouth, facial swelling
- Respiratory compromise wheezing, dyspnea, stridor or hypoxia
 (O2 saturation < 90%)
- BP < 90 mmHg SBP or >30% decrease from patient baseline



Start basic life support:

- High oxygen flow
- On bed, head down, legs up
- Large bore IV cannula, 1 L normal saline STAT
- Initiate vital signs at least every 15 minutes



Consider (under medial direction):

Epinephrine 1:1000

• 0.3 mg (0.3 mL) IM into lateral thigh



Airway Threatened: Nebulized epinephrine 1:1000, 3–5 mL (3–5 mg)

Bronchospasm: Nebulized salbutamol 5 mg

(Wheeze or Hypoxia) Consider: Intubation / nebulized epinephrine

Hypotension: Place on cardiac monitor

(Systolic BP <100 mmHg) Further epinephrine 1:1000, 0.3 mg IM and

IV normal saline bolus 20 mL/kg STAT as needed

Have vasopressin on hand



Transfer to Emergency Room/ICU Observe until all symptoms resolved.

Table 5: Grading and Management of Allergic or Infusion-Related Reactions

Adverse Event	Grade						
	1	2	3	4	5		
Infusion- Related Reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids): prophylactic medications indicated for ≤ 24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement, hospitalization indicated for clinical sequelae	Life- threatening consequences; urgent intervention required	Death		
Allergic Reaction	Transient flushing or rash, drug fever < 38.0°C. Intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids): prophylactic medications indicated for ≤ 24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement, hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life- threatening consequences; urgent intervention required	Death		
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticarial; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life- threatening consequences; urgent intervention required	Death		
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids): prophylactic medications indicated for ≤ 24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement, hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life- threatening consequences; pressor or ventilator support indicated	Death		

Abstracted from NCI CTCAE Version 4.03.

9.6.2 Potential Immune Effects

An antibody blocking FcRn is anticipated to have several effects. These include acceleration of catabolism of IgG, but not other immunoglobulin isotypes such as IgA and IgM, leading to dose-dependent decreases in circulating IgG levels by up to an estimated 50% from the baseline levels after a single dose and further decreases after multiple doses up to a 70% to 80% reduction. Based on studies in humans, it is expected that with a single dose, the nadir of this effect will occur approximately 5 days after dosing. The time course of recovery of IgG following dosing in the Phase 1a study suggests that a return to within normal limits occurs within 4 weeks after a single dose and within 4 weeks after multiple doses as shown in NHPs.

Given the normal adult range of IgG of 700 to 1600 mg/dL (in some references), with a mean of 1150 mg/dL, a 50% decrease in the mean would be to 575 mg/dL and a 50% decrease from the low end of the normal range of 700 mg/dL would be to 350 mg/dL. An 80% decrease from baseline after multiple doses would result in IgG levels of 230 mg/dL and 140 mg/dL, respectively. While these levels are in the range found in patients with primary humoral immunodeficiency [Ameratunga 2013], the levels will be transient. Study subjects will be monitored clinically for any infection. Further, commercial IVIG can be given to reverse the low IgG levels in case of a bacterial infection occurring while their IgG levels are decreased.

An antibody blocking FcRn is expected to also down modulate innate and adaptive immunity and the catabolism of IgG-containing immune complexes (IC). Specifically, it is expected that anti-FcRn will promote the clearance of IgG-containing ICs and the effects of these IC on stimulating innate immune cell production of inflammatory cytokines (e.g., IL-12, interferon-γ, and tumor necrosis factor [TNF]) and inhibit the processing and presentation of antigens contained within IC and thus the antigen-specific activation of CD4⁺ and CD8⁺ T-cells. Therefore, subjects with pre-existing conditions that are dependent upon IgG antibodies, such as chronic infections (e.g., HIV, HBV or HCV), will be excluded from this study, as will subjects with active infection in general.

SYNT001 administration could decrease the level of protective antibodies from prior vaccinations. Protective antibody levels for tetanus and varicella-zoster virus (chickenpox) are to be tested in accordance with Section 6.7.3.

10 CONCOMITANT MEDICATION AND TREATMENT

All treatments a subject receives within 14 days prior to enrollment through the end of the study (Day 56) will be documented. Concomitant medication and treatment for co-existing conditions, including those for pemphigus, are permitted if not excluded below. Topical antibiotics are permitted to treat active infections that occur on study. Topical or systemic treatments for oral candidiasis are permitted. Topical lidocaine for transient pain relief is acceptable as needed. Significant increases in anti-pemphigus medications may result in subjects being discontinued from the study. Concomitant treatment that is medically indicated for any AEs the subject experiences during the study are permitted

Use of the following treatments will not be permitted during the study unless otherwise specified:

- Rituximab or other anti-CD20 antibody
- Monoclonal antibodies other than study drug
- Any immunosuppressive drugs apart from corticosteroids, azathioprine, mycophenolate mofetil, or cyclosporine.
- Topical steroids
- Any dietary herbal supplements
- Any investigational drug or device
- Any vaccinations

If over a period of at least two weeks on study drug, a subject on corticosteroids shows the absence of new lesions and significant healing of lesions that existed at study baseline, a slow corticosteroid taper may be started as per the following suggested schedule

- If on > 30 mg of prednisone per day, decrease by 10 mg every two weeks until a dose of 30 mg per day then decrease by 5 mg every two weeks
- If on < 30 mg of prednisone per day, decrease by 5 mg every two weeks

In cases in which concomitant medications are used, details to be recorded include the following: medication name, start date and time, stop date and time, dose, route, frequency, and reason for use. The concomitant medication names are to be coded using the World Health Organization

(WHO) Drug Dictionary (WHO-DD March 2013, Type B2 or later) and classified by anatomical therapeutic chemical (ATC) categories.

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11 SAFETY

11.1 Safety Parameters

Clinical and laboratory AEs will be graded using the NCI CTCAE; Version 4.03 (See Appendix A).

Subjects will be monitored throughout the treatment and follow-up period for occurrence of AEs (acute, delayed, and/or cumulative), as well as for changes in clinical status, vital sign measurements, and laboratory data (including PD). Safety parameters to be measured/assessed include PEs, vital sign measurements, hematology, serum chemistries, urinalysis, and ECG.

11.2 Adverse Event Definition

An AE is defined as any untoward medical occurrence in a clinical trial subject associated with the use of a drug, whether considered drug related. An AE can be an unfavorable and unintended sign (e.g., an abnormal laboratory value finding), a symptom, or a disease temporally associated with the use of a drug, without judgment as to causality. An AE can arise from use of the drug (e.g., use in combination with another drug) and from any route of administration, formulation or dose, including an overdose. An AE also includes, but is not limited to, any clinically significant worsening of a pre-existing condition. Examples include:

- Any sign, symptom, physical finding, or laboratory result that has worsened in nature, severity or frequency compared to baseline;
- Reactions from an investigational drug, including those occurring because of an overdose, abuse of the study drug, withdrawal phenomena, sensitivity or toxicity;
- Concurrent illness that was not present or worsens in nature, severity, or frequency compared to baseline;
- Injury or accident; and/or
- Exacerbation of a pre-existing condition.

For data collection, all untoward events that occur after informed consent through 28 days after study drug dosing are to be recorded on eCRFs by the investigational site.

While pregnancy alone is not considered as an AE or SAE, any pregnancy complication(s) should be recorded as an AE(s) or SAE(s) (if applicable). Elective abortions without complications should not be regarded as AEs, unless they were therapeutic abortions (see below). Hospitalization for normal delivery of a healthy newborn should not be considered an SAE. If a female subject becomes pregnant during the conduct of the study, the Investigator must notify the Sponsor according to the procedures provided in Section 11.3.8).

11.3 Evaluating Adverse Events

The Investigator will determine the seriousness, intensity, and causality of an AE associated with the use of the study drug (i.e., events where there is a reasonable possibility that the event may have been caused by the study drug) based on the definitions that follow.

11.3.1 Serious Adverse Events

(Notify Medpace Safety within 24 hours; document on eCRF)

The SAE definition and reporting requirements are in accordance with Title 21 Part Code of Federal Regulations (CFR) 312.32 and the Guidance for Industry and Investigators Safety Reporting Requirements for Investigational New Drug (INDs) and Bioavailability /Bioequivalence Studies.

SAE: An AE is considered "serious" if, in the view of either the Investigator or sponsor, it results in any of the following outcomes:

• <u>Death:</u> This includes any death that occurs while the subject is "on study" as well as any death that occurs within 28 days after study drug administration.

Note: Death is an outcome of an AE, and not an AE. The event(s) that caused death (e.g., illness, accident) is the SAE. Death due to any other cause(s) must also be reported as an outcome of the reportable SAE.

- <u>Life-threatening adverse drug event:</u> An AE or suspected adverse reaction is considered "life threatening" if, in the view of either the Investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization:

In the absence of an AE, the Investigator should not report hospitalization or prolongation of hospitalization. This is the case in the following situations:

- Hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol
- Hospitalization or prolongation of hospitalization is part of routine procedure followed by study center

- Hospitalization for survey visits or annual physicals
- Hospitalization for observation with release within 24 hours

In addition, a hospitalization planned before the start of the study for a pre-existing condition, which has not worsened, does not count as an SAE.

• Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- Congenital anomaly/birth defect
- <u>Important medical event:</u> An event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

11.3.2 Overdose

An overdose is defined as a significant variation from the recommended/scheduled dosage for a product. The dosing for this study will be conducted in a controlled clinical setting and an overdose is not anticipated. However, in the event of an accident, for this study, an overdose of SYNT001 is considered a dose that is two-fold higher than the intended dose for the subject.

11.3.3 Non-Serious Adverse Events

(Document on eCRF)

All other AEs, not fulfilling the previous definitions, are classified as non-serious.

11.3.4 Protocol-Related Adverse Events

AEs that are not test drug related may nevertheless be considered by the Investigator or the Medical Monitor to be related to the conduct of the clinical study. That is, the event may be related to the fact that a subject is participating in the study. For example, a protocol-related AE may be an event that occurs during a screening period or that is related to a procedure required by the protocol.

11.3.5 Assessment of Causality

A medically qualified Investigator must assess the relationship of any AE (including SAEs) to the use of the investigational product, as related or not related, based on clinical judgment and using all available information, and may include consideration of the following factors:

- Possible alternative causes of the AE, including the disease under treatment, pre-existing conditions, concomitant use of other drugs, and presence of environmental or genetic factors.
- The temporal association between drug exposure and onset of the AE.
- Whether the manifestations of the AE are consistent with known actions or toxicity of the investigational product.
- The AE resolved or improved with decreasing the dose or stopping use of the investigational product (dechallenge). Judgment should be used if multiple products are discontinued at the same time.

The causal relationship between the study medication and the AE will be assessed using one of the following categories:

Not Related: Factors consistent with an assessment of Not Related include:

- Temporal relationship is lacking (e.g., the event did not occur within a reasonable time frame following administration of the study medication); or
- Other causative factors more likely explain the event (e.g., a pre-existing condition, other concomitant treatments).

Related: Factors consistent with an assessment of Related include:

• There is a positive temporal relationship (e.g., the event occurred within a reasonable time frame following administration of study medication); or

The AE is more likely explained by the investigational product than by another cause (i.e., the AE shows a pattern consistent with previous knowledge of the investigational product or the class of the investigational product)

11.3.6 Recording Adverse Events

All AEs (including SAEs) are to be accurately recorded on the <u>Adverse Event</u> page of the subject's eCRF. The severity of each AE will be graded using the NCI CTCAE, Version 4.03. The date of onset as well as the end date of the event also should be recorded or the event should be entered as "ongoing". In addition, the method used to treat the AE and the outcome of the AE also will be noted. The Investigator will assess the relationship of the event to study drug.

11.3.7 Planned Hospitalization

A hospitalization planned by the subject prior to the first dose of study medication is considered a therapeutic intervention and not the result of a new SAE and should be recorded as medical

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history. If the planned hospitalization or procedure is executed as planned, the record in the subject's medical history is considered complete. However, if the event/condition worsens during the trial, it must be reported as an AE.

11.3.8 Reporting Pregnancies

If a female subject or the female partner of a male subject becomes pregnant during the course of the study, the Investigator must report the pregnancy to the Medpace Safety using the **Pregnancy Reporting Form** within **24 hours** of becoming aware of the event. The Investigator must obtain consent to collect pregnancy information (including the status of the newborn, if applicable).

If some of the information required for completion of the Pregnancy Reporting Form is unavailable at the time of the initial report, follow-up reports will be completed and submitted within 24 hours of becoming aware of the new information. Any pregnancy will be followed through delivery for the observation of any SAEs. Any SAE that occurs during pregnancy must be recorded on the SAE report form in the EDC system (e.g., maternal serious complications, therapeutic or spontaneous abortion, ectopic pregnancy, stillbirth, neonatal death, congenital abnormality, birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs (See Section 11.3.9).

11.3.9 Serious Adverse Event Reporting

11.3.9.1 Governing Regulatory Requirements

Compliance with this request for prompt reporting is essential in that the sponsor is responsible for informing the US Food and Drug Administration (FDA) and other regulatory authorities as well as all other participating Investigators of the event.

Under FDA ruling (US Code of Federal Regulations, Title 21 CFR Part 312.32) and the ICH Guidelines for Clinical Safety Data Management Definitions and Standards for Expedited Reporting, the sponsor is required to submit written documentation, in the form of a safety report, detailing:

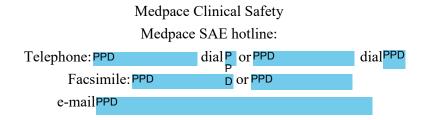
- Any event associated with the use of the drug, that is both serious and unexpected, or
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects, including reports of <u>mutagenicity</u>, <u>teratogenicity</u>, <u>or carcinogenicity</u>.

Written submission must be made by the sponsor to the FDA and the IRBs as soon as possible and in no event later than 15 calendar days after the sponsor's initial notification of the event. The sponsor shall also inform all Investigators.

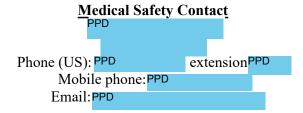
11.3.9.2 Time Frame for Reporting

Any death, SAE, pregnancy, or unexpected (and severe) AE experienced by the subject after informed consent or within 28 days of receiving study drug, regardless of relationship to study drug, or any death that occurs more than 28 days after receiving study drug, and is believed to be study drug related, must be promptly reported (within 24 hours of the Investigator becoming aware of the event) by telephone or electronic transmission to the sponsor (or designee).

Contact information for **SAE** reporting:



Additionally, the Investigator will be able to contact the **Medical Monitor**:



11.3.9.3 Information to be Provided by the Investigator

SAEs must be recorded on the SAE form in the EDC system. This requirement includes all SAEs that occur after informed consent and through 28 days after study drug dosing, and in addition, any SAE that are assessed as related to study treatment by the Investigator, even if the SAE occurs more than 28 days after study drug dosing.

The minimum information required for SAE reporting includes identity of Investigator, site number, subject number, an event description, SAE term(s), onset date, the reason why the event is serious (i.e., the seriousness criteria) and the Investigator's assessment of the relationship of the event to study treatment. Additional SAE information including medications or other therapeutic measures used to treat the event, action taken with the study treatment due to the event, and the outcome/resolution of the event will be recorded. Paper forms for reporting SAEs will be provided to the study sites as back-up in case the EDC system is not accessible.

In all cases, the Investigator should continue to monitor the clinical situation and report all material facts relating to the progression or outcome of the SAE. Furthermore, the Investigator may be required to provide supplementary information as requested by Syntimmune or designee.

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When reporting an SAE, the following additional points should be noted:

- When the diagnosis of an SAE is known or suspected, the Investigator should report the
 diagnosis or syndrome as the primary SAE term, rather than as signs or symptoms. Signs
 and symptoms may then be described in the event description. For example, dyspnea
 should not be used as an SAE term if the diagnosis, which caused the dyspnea, is known
 to be malignant pleural effusion.
- Death should not be reported as an SAE, but as an outcome of a specific SAE, unless the event preceding the death is unknown. In the exceptional case where the events leading to death are unknown, then death may be used as an event term. If an autopsy was performed, the autopsy report should be provided.
- While most hospitalizations necessitate reporting of an SAE, some hospitalizations do not require SAE reporting, as follows:
 - Elective or previously scheduled surgery, e.g., a previously scheduled ventral hernia repair
 - Procedures for pre-existing conditions that have not worsened after initiation of treatment
 - Pre-specified study hospitalizations for observation
 - Events that result in hospital stays of less than 24 hours and that do not require admission, e.g., an emergency room visit for hematuria that results in a diagnosis of cystitis and discharge to home on oral antibiotics
- SAEs must, however, be reported for any surgical or procedural complication resulting in prolongation of the hospitalization.

11.3.10 Regulatory Reporting

Syntimmune (or designee) will process and evaluate all SAEs as soon as the reports are received. For each SAE received, Syntimmune will decide as to whether the criteria for expedited reporting have been met.

Syntimmune (or designee) will submit SAEs that meet the criteria for expedited reporting to the regulatory authorities in accordance with local regulations governing safety reporting. Reporting of SAEs by the Investigator to his or her IRB will be done in accordance with the standard operating procedures and policies of the IRB. Adequate documentation must be maintained showing that the IRB was properly notified.

11.3.11 Follow-up Information on a Serious Adverse Event (SAE)

Appropriate diagnostic tests should be performed and therapeutic measures, if indicated, should be instituted. Appropriate consultation and follow-up evaluations should be carried out until the event has returned to baseline or is otherwise explained by the Investigator.

If all required information on the SAE form is not available at the time of the initial report, follow-up information will be completed in the EDC system.

11.4 Other Safety Considerations

11.4.1 Laboratory Data

All laboratory data obtained during the study should be reviewed. Any abnormal value that leads to a change in subject management (e.g., requirement for additional medication or monitoring) or is of clinical significance by the Investigator should be reported as an AE and/or SAE as appropriate, unless this value is consistent with values obtained before entry into the study.

11.4.2 Medication Errors

Any medication error that results in an AE, even if it does not meet the definition of serious, requires reporting within 24 hours to the safety Medical Monitor.

11.4.3 Follow-Up of Adverse Events

Any SAE or AE assessed as related that led to treatment discontinuation (including clinically significant abnormal laboratory values that meet these criteria) and ongoing 28 days after study drug dosing must be followed until either resolution of the event or determination by the Investigator that the event has become stable or irreversible. This follow-up guidance also applies to related SAE that occur more than 28 days after study drug dosing. The status of all other continuing AEs will be documented as of 28 days after study drug dosing. The Investigator will follow all subjects who experience AEs until there is a return to the subject's baseline condition, or until a clinically satisfactory resolution has been achieved. The appropriate follow-up visits must be scheduled and the specific tests repeated or performed as necessary.

Where a diagnosis is possible, it is preferable to report this diagnosis rather than a series of terms (signs/symptoms) relating to the diagnosis.

11.5 Safety Monitoring for Dose Escalation

Following dosing in each cohort, all safety/tolerability data (e.g., PEs, vital signs [including pulse oximetry], clinical safety laboratory tests, ECGs and AE/SAE assessments) as well as any available and relevant PD data collected through Day 42 will be reviewed by the DEC. A decision to escalate to the next cohort will be made. The recommendation may be to continue to the next scheduled dose level, discontinue the study or to modify dosing to a dose less than the current dose or higher than the current dose but lower than the next planned dose.

12 STATISTICAL CONSIDERATIONS

All descriptive and inferential statistical analyses will be performed using the most recently released and available Statistical Analysis System (SAS) software, unless otherwise noted. Missing data will not be imputed unless otherwise stated. All clinical data captured will be provided in data listings. A Statistical Analysis Plan (SAP) and a Pharmacokinetic Analysis Plan (PAP) will be finalized prior to database lock.

12.1 General Design

All data for enrolled subjects will be presented in data listings by subject number.

Continuous data will be described using descriptive statistics: number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Frequencies and percentages will be used for summarizing discrete (categorical) data. When categorical data are presented, the percent will be suppressed when the count is zero to draw attention to the non-zero counts. The denominator for all percentages, unless otherwise specified, will be the number of subjects in the specified analysis population.

12.2 Sample Size Justification

Formal sample size calculations were not performed. The number of subjects was chosen based on feasibility and was considered sufficient to meet the study objectives.

12.3 Statistical Considerations

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP). The SAP may modify the plans outlined in the protocol; any deviations from the previously described statistical plan will be described and justified in an SAP amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate and will be described in the SAP. Methods of handling of missing data for different endpoints will be further specified in the SAP. In general, where individual data points are missing because of insufficient samples, dropouts, or other reasons, the data will be analyzed based on reduced denominators unless specified otherwise in the SAP.

Results will be summarized by cohorts.

12.3.1 Study Populations

Three populations will be employed in the analysis of study data:

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- The **intent-to-treat (ITT)** population will consist of all subjects who have received at least one dose of study drug. All safety analyses will be performed on the ITT population.
- The **PK** population will consist of all subjects who receive at least one dose of study drug and have sufficient post-dose blood samples to obtain PK parameters.
- The **PD** population will consist of all subjects who receive at least one dose of study drug and have post-dose PD data available.

Primary safety analyses will be performed on the ITT population. Demographics, subject disposition, and screening and baseline characteristics will be summarized for the ITT, PK, and PD populations, where appropriate.

12.3.2 Subject Accountability, Demographics, and Baseline Characteristics

Subject disposition, demographic information and baseline characteristics will be presented. Any discrepancy between treatment to be given and treatment received will be accounted for in these displays.

12.3.3 Concomitant Medications

Concomitant medications will be coded using WHO Drug Dictionary (WHO-DD March 2013, Type B2 or later) and the data will be summarized and presented in tables and listings.

12.4 Planned PK Analysis

Study drug concentrations will be used to calculate the following PK parameters: $t_{1/2}$, C_{max} , T_{max} , and AUC_{0-24} and $AUC_{0-\infty}$. PK parameters will be determined using noncompartmental method(s). Descriptive statistics of PK parameters for SYNT001 will include mean, SD, coefficient of variation (CV), median, minimum, and maximum. T_{max} will be reported as median and range. All descriptive statistics will be performed on untransformed PK parameters and after log_{10} transformation of PK parameters.

For calculation of mean concentrations and generation of mean concentration-time profiles, all below the limit of quantification (BLQ) values will be set to zero except when an individual BLQ falls between 2 quantifiable values, in which case it will be omitted.

If there are values above the BLQ, but too sparse to allow full analysis, descriptive statistics will be performed on available values.

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12.5 Safety Data

Safety observations and measurements include AEs, safety laboratory tests, vital sign measurements, PEs, and ECGs.

Treatment-emergent AEs will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA®; Version 19 or higher) System Organ Class (SOC) and preferred term, classified from verbatim terms. The incidence and percentage of subjects with at least 1 occurrence of a preferred term will be included, using the most severe grade. The number of events per preferred term will also be summarized. Causality (relationship to study treatment) will be summarized separately.

AEs, SAEs, and AEs leading to withdrawal, dose modification, or treatment discontinuation will be listed by subject, cohort, and overall per SOC and preferred terms. Duration of AEs will be determined and included in listings, along with action taken and outcome.

Laboratory results will be summarized by cohort. Incidence of laboratory abnormalities will be summarized. The worst on-study grade after the first dose of study drug will be summarized. Results for variables that are not coded will be presented in the listings as below, within, and above the normal limits of the local laboratory.

Vital sign measurements and change from baseline will be summarized at each scheduled time point by cohort using descriptive statistics.

Arithmetic mean of parameters from triplicate ECG will be calculated first for each participant at each planned time point. Then summary statistics of ECG test parameters (mean of triplicate) and change from baseline to each post-dose time point will be calculated. Shift tables for ECG test result category change (normal, abnormal, clinically abnormal) from pre-dose to each post-dose time point showing number and percentage of subjects with movement between categories will be presented by treatment group. Frequency and percentage of subjects experiencing potential QTc prolongation (QTcF > 450) will be summarized at each time point by cohort.

12.6 Pharmacodynamic/Activity Data

PD results will be summarized by cohort.

12.7 Immunogenicity Data

Immunogenicity results will be summarized by cohort.

12.8 Interim Analysis

No interim analysis is planned. Safety results will be examined for making dose-escalation decisions; no statistical analyses are planned for aiding these dose-escalation decisions.

13 DATA QUALITY ASSURANCE

All data will be entered in a validated electronic data capture system using single data entry. Standard procedures (including following data review guidelines, manual clinical review based on subject profiles, computerized validation to produce queries, and maintenance of an audit file which includes all database modifications) will be followed to ensure accurate data. Clinical personnel will review all data listings for outliers, data inconsistencies, and spelling errors.

During the study, a study site monitor will make site visits to review protocol compliance, compare electronic case report forms (eCRFs) against individual subject medical records, assess drug accountability, and ensure that the study is being conducted using pertinent regulatory requirements. eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that subject confidentiality is maintained. Checking the eCRFs for completeness, clarity and cross checking with source documents is required to monitor the progress of the study. Direct access to source data is also required for inspections and audits, and will be carried out giving due consideration to data protection and medical confidentiality. Each Investigator will have assured Syntimmune of full access to complete source data for study participants and associated necessary support at all times.

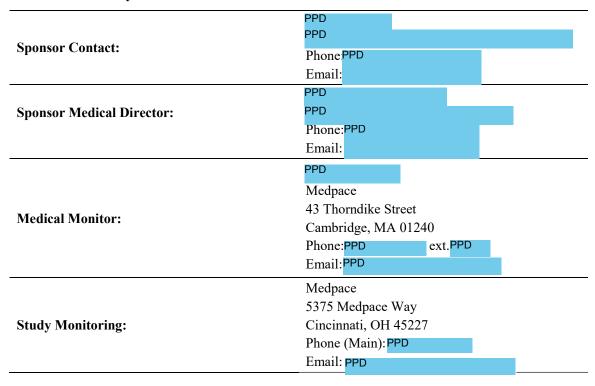
In addition to routine monitoring procedures, audits of clinical research activities in accordance with standard operating procedures (SOPs) may be performed to evaluate compliance with the principles of GCP. A regulatory authority may also wish to conduct an inspection (during the study or even after its completion). If a regulatory authority requests an inspection, the Investigator must immediately inform Syntimmune that this request has been made. Study conduct may be assessed during the study by a Clinical Quality Assurance representative(s) to ensure that the study is conducted in compliance with the protocol. This designee, as well as the site monitor, will be permitted to inspect the study documents (study protocol, eCRFs, investigational product accountability, original study-relevant medical records). All subject data will be treated confidentially. During the clinical study, access will be available to Syntimmune or their designee (e.g., contract research organization [CRO]) to view the eCRFs after completion of the individual sections of the study. Furthermore, the study protocol, each step of the data-recording procedure and the handling of the data as well as the study report may be subject to independent review by a Quality Assurance representative. Clinical site and study audits will be conducted as necessary to assure the validity of the study data.

14 STUDY ADMINISTRATION

14.1 Study Administrative Structure

The study administration structure is provided in Table 6.

Table 6: Study Administrative Structure



14.2 Ethical Conduct of the Study

The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH E6 Tripartite Guideline (January 1997), and in general, be conducted in a manner consistent with the principles described in the Declaration of Helsinki. The Investigator will ensure that the conduct of the study complies with the basic principles of GCP as outlined in the current version of 21 CFR, subpart D, Part 312, "Responsibilities of Sponsors and Investigators", Part 50, "Protection of Human Subjects", and Part 56, "Institutional Review Boards".

14.3 Informed Consent (ICF)

A properly executed, written informed consent document, in compliance with 21 CFR, Part 50 and the ICH guidelines, will be obtained from each subject before the subject is entered into the study and before any study screening procedure is performed that involves risk. Attention will

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be directed to the basic elements required for incorporation into the informed consent under US Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a]) and (21 CFR 50.25[b]), as necessary.

Sample ICFs will be supplied to each site. Syntimmune or its designee must review any proposed deviations from the sample ICF. The final IRB-approved document must be provided to Syntimmune for regulatory purposes.

It is the responsibility of the Investigator, or a person designated by the Investigator, to obtain written informed consent from each subject (or the subject's legally authorized representative) participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. In the case where the subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the subject has orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. A copy of the ICF must be provided to the subject or to the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

The eCRF for this study contains a section for documenting informed subject consent, and this must be completed appropriately. Signed ICFs must remain in each subject's study file and must be available for verification by site monitors at any time. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated as necessary. All subjects (including those already being treated) should be informed of the new information, should be given a copy of the revised form, and should give their consent to continue in the study.

14.4 Institutional Review Board

This study is being conducted under US IND 128152. This protocol (and any modifications) and appropriate consent procedures must be reviewed and approved by an IRB. This board must operate in accordance with the current federal or local regulations. The Investigator will send a letter or certificate of IRB approval to Syntimmune (or designee) before subject enrollment and whenever subsequent modifications to the protocol are made.

14.5 Dose Escalation Committee

The DEC will be responsible for confirming the safety of the investigative product prior to dose escalation, as well as the dose level for each successive cohort. In addition, over the course

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of the study, the DEC will review any drug-related SAEs to determine if modifications to the study or other measures are necessary to ensure the safety of the subjects. The DEC will consist of the Medical Monitor, an Independent Clinical Expert and a Syntimmune Medical Officer. To assist in the safety assessments, the DEC may request that Investigators, other experts, or members within their organizations review the data and participate in the discussions.

14.6 Future Use of Subject Samples

Not all the tissue and blood components obtained during this study may be required for the tests that are part of the clinical trial. Available samples may be used for additional research. This research will help to understand disease subtypes, drug response and AE, and possibly identify new drug targets or biomarkers that predict subject response to treatment. The use of the samples for internal research will be done using the guidelines defined by the FDA guidance for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individual Identifiable (issued 25 April 2006) and the European Medicines Agency (EMA) Reflection Paper on Pharmacogenetic Samples, Testing and Data Handling (Doc. Ref.

EMEA/CHMP/PGxWP/201914/2006; 15 November 2007). If a subject requests destruction of their tissue and blood samples and the samples have not yet been de-identified, Syntimmune will destroy the samples as described in this FDA guidance. Syntimmune will notify the Investigator in writing that the samples have been destroyed.

15 CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications to ongoing studies must be made only after consultation between a Syntimmune representative and the Investigator. Protocol modifications will be prepared, reviewed, and approved by Syntimmune representatives.

All protocol modifications must be submitted to the IRB for information and approval in accordance with local requirements, and to regulatory agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study subjects, or when the change involves only logistical or administrative aspects of the trial (e.g., change in site monitor, change of telephone number).

16 CONDITIONS FOR TERMINATING THE STUDY

Syntimmune has the right to terminate the study at any time. In terminating the study, Syntimmune and the Investigator will ensure that adequate consideration is given to the protection of the subjects' interests.

17 STUDY DOCUMENTATION, CRFS, AND RECORD KEEPING

17.1 Investigator's Files and Retention of Documents

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into 2 separate categories as follows: (1) Investigator's study file and (2) subject clinical source documents.

The Investigator's study file will contain the protocol and protocol amendments, eCRFs, query forms, IRB and governmental approval with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Subject clinical source documents (usually predefined by the project to record key efficacy and safety parameters independent of the eCRFs) may include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalogram, X-ray, pathology and special assessment reports, signed ICFs, consultant letters, and subject screening and enrollment logs. The Investigator must keep these 2 categories of documents on file for at least 2 years following the marketing application approval date for the study treatment and for the indication being investigated or for 2 years after the development program is discontinued and the FDA notified. After that period, the documents may be destroyed subject to local regulations with prior written permission from Syntimmune. If the Investigator wants to assign the study records to another party or move them to another location, Syntimmune must be notified in advance.

If the Investigator cannot guarantee the archiving requirement at the study site for any or all of the documents, special arrangements must be made between the Investigator and Syntimmune to store these in a sealed container outside of the study site so that they can be returned sealed to the Investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the study site.

17.2 Source Documents and Background Data

Investigators must maintain adequate and accurate source documents on which the eCRFs for each subject are based. They are separate and distinct from the eCRFs.

These records include detailed notes on the following:

- Medical history
- Date and time of informed consent with Health Insurance Portability and Accountability
 Act (HIPAA) authorization either contained in the ICF or presented to the subject
 candidate as a standalone document
- Description of the complete consenting process
- The basic identifying information that linked the subject's medical record with the eCRFs
- The results of all diagnostic tests performed, diagnoses made, therapy provided, and any other data on the condition of the subject
- The medical condition of the subject during their involvement in the study
- All AEs
- The subject's exposure to the study medication
- The subject's exposure to any concomitant therapy
- All relevant observations and data on the condition of the subject throughout the trial
- Justification for all entries in the subject's eCRF

A subject log of all potentially eligible subjects considered, but not consented, for obvious deviations from the entry criteria, will be kept at each site. The log will contain subjects' initials, diagnosis, eligibility, or, if not eligible, reason for not consenting. All consented subjects will be logged, regardless of whether they ultimately enroll.

Upon request, the Investigator will supply Syntimmune with any required background data from the study documentation or clinic records. This is particularly important when eCRFs are illegible or when errors in data transcription are suspected. In case of special problems or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

17.3 Audits and Inspections

The Investigator should understand that source documents for this study should be made available to appropriately qualified personnel from Syntimmune (or designee), or to health authority inspectors after appropriate notification. The verification of the eCRF data must be by direct inspection of source documents.

17.4 Electronic Case Report Forms

Clinical trial data for this study will be captured on eCRF designed for computer processing and analysis. This computerized system will be validated and compliant with 21 CFR Part 11. Corrections to data will be made using 21 CFR Part 11, Electronic Records; Electronic Signatures. If corrections are made after review and sign-off by the Investigator, he/she must be aware of the changes and provide written acknowledgement. There will also be an electronic audit trail. Corrections on paper CRFs must be initialed and dated by the person making the change. The Investigator agrees to provide all information requested on the eCRF in an accurate manner using instructions provided. The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to Syntimmune in the eCRF and in all required reports.

An eCRF is required to be submitted for every subject who receives any amount of study drug. This includes submission of retrievable data on subjects who withdraw before completion of the study. Prior to submission, eCRFs must be reviewed for completeness and accuracy, and signed and dated where either indicated, by the Principal Investigator or authorized delegate from the study staff. If a subject stops treatment or terminates from the study, the dates and reasons must be noted on the eCRF.

18 MONITORING THE STUDY

It is understood that the responsible Syntimmune site monitor (or designee) will contact and visit the Investigator regularly and will be allowed on request to inspect the various records of the trial (eCRFs and other pertinent data) if subject confidentiality is maintained in accordance with local requirements.

It will be the site monitor's responsibility to inspect the eCRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The site monitor should have access to laboratory test reports and other subject records needed to verify the entries on the eCRF. The Investigator (or designee) must agree to cooperate with the site monitor to ensure that any problems detected during these monitoring visits are resolved.

19 CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The Investigator must ensure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On eCRFs or other documents submitted to Syntimmune, subjects should be identified by an identification code and not by their names. The Investigator should keep a subject enrollment log showing codes, names, and addresses. The Investigator should maintain documents not for submission to Syntimmune (e.g., subjects' written consent forms) in strict confidence.

Authorized regulatory officials and Syntimmune personnel (or their representatives) will be allowed full access to inspect and copy the records. All study drugs, subject bodily fluids and tissue, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by Syntimmune.

The Principal Investigator also agrees that all information received from Syntimmune, including but not limited to the IB, this protocol, eCRFs, the INDs, and any other study information remain the sole and exclusive property of Syntimmune during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The Principal Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

20 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. The Investigator agrees that any manuscript or abstract they author may be published only after receiving written permission from Syntimmune.

If Syntimmune coordinates a publication or presentation of study results from all study sites, the participation of Investigator or other representatives of study site as a named author shall be determined in accordance with Syntimmune policy and generally accepted standards for authorship.

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Appendix A: NCI CTCAE, Version 4.03

Common Terminology Criteria for Adverse Events (CTCAE)

Version 4.0

Published: May 28, 2009 (v4.03: June 14, 2010)

U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health National Cancer Institute

Common Terminology Criteria for Adverse Events v4.0 (CTCAE) Publish Date: May 28, 2009

Quick Deference

The NCI Common Terminology Criteria for A brief definition is provided Adverse Events is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

System Organ Class, the highest level of the MedDRA hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e.g., SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

CTCAE Terms

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v4.0 term is a MedDRA LLT (Lowest A Semi-colon indicates 'or' within the description Level Term).

Definitions

to clarify the meaning of each AE term.

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical and therefore is not an option. descriptions of severity for each AE based on this general guideline:

Grade 1 Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not

noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.

Life-threatening Grade 4 consequences: urgent intervention indicated.

Grade 5 Death related to AE.

of the grade.

A single dash (-) indicates a grade is not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and Grade 2 Moderate; minimal, local or undressing, feeding self, using the toilet, taking medications, and not bedridden.

⁺ CTCAE v4.0 incorporates certain elements of the MedDRA terminology. For further details on MedDRA refer to the MedDRA MSSO Web site (http://www.meddramsso.com).

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	В	lood and lymphatic system	em disorders		
			Grade	T	
Adverse Event	1	2	3	4	5
nemia	Hemoglobin (Hgb) <lln -="" 10.0="" 100="" 6.2="" <lln="" dl;="" g="" l;="" l<="" mmol="" td=""><td>Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L</td><td>Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated</td><td>Life-threatening consequences; urgent intervention indicated</td><td>Death</td></lln>	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
	ted by an reduction in the amount of the palpitations of the heart, soft syst	•	• • •	ay include pallor of the skin and m	nucous
Bone marrow hypocellular	Mildly hypocellular or <=25% reduction from normal cellularity for age	Moderately hypocellular or >25 - <50% reduction from normal cellularity for age	Severely hypocellular or >50 - <=75% reduction cellularity from normal for age	Aplastic persistent for longer than 2 weeks	Death
Definition: A disorder characteriz	ed by the inability of the bone mar	row to produce hematopoietic ele	ments.		
Disseminated intravascular coagulation	-	Laboratory findings with no bleeding	Laboratory findings and bleeding	Life-threatening consequences; urgent intervention indicated	Death
	red by systemic pathological activa s depleted of platelets and coagula		which results in clot formation thro	oughout the body. There is an inci	ease in the
Febrile neutropenia	-	-	ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour.	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz degrees F) for more than one ho	ed by an ANC <1000/mm3 and a sour.	single temperature of >38.3 degre	es C (101 degrees F) or a sustaine	ed temperature of >=38 degrees 0	C (100.4
Hemolysis	Laboratory evidence of hemolysis only (e.g., direct antiglobulin test; DAT; Coombs'; schistocytes; decreased haptoglobin)	Evidence of hemolysis and >=2 gm decrease in hemoglobin.	Transfusion or medical intervention indicated (e.g., steroids)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by laboratory test results that in	ndicate widespread erythrocyte ce	Il membrane destruction.		
Hemolytic uremic syndrome	Evidence of RBC destruction (schistocytosis) without clinical consequences	-	Laboratory findings with clinical consequences (e.g., renal insufficiency, petechiae)	Life-threatening consequences, (e.g., CNS hemorrhage or thrombosis/embolism or renal failure)	Death
Definition: A disorder characteriz	ed by a form of thrombotic microal	ngiopathy with renal failure, hemo	lytic anemia, and severe thromboo	cytopenia.	
Leukocytosis	-	-	>100,000/mm3	Clinical manifestations of leucostasis; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by laboratory test results that ir	ndicate an increased number of w	nite blood cells in the blood.		
Lymph node pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by a sensation of marked disco	mfort in a lymph node.			
Spleen disorder	Incidental findings (e.g., Howell- Jolly bodies); mild degree of thrombocytosis and leukocytosis	Prophylactic antibiotics indicated	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder of the splee	en.		_	_	
Thrombotic thrombocytopenic purpura	Evidence of RBC destruction (schistocytosis) without clinical consequences	-	Laboratory findings with clinical consequences (e.g., renal insufficiency, petechiae)	Life-threatening consequences, (e.g., CNS hemorrhage or thrombosis/embolism or renal failure)	Death
	ted by the presence of microangiop	•	cytopenic purpura, fever, renal abr	normalities and neurological abnor	malities suc
	ual disturbances. It is an acute or s	subacute condition.	Τ	Τ	1
Blood and lymphatic system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Cardiac disorders							
	Grade						
Adverse Event	1	2	3	4	5		
Acute coronary syndrome	-	Symptomatic, progressive angina; cardiac enzymes normal; hemodynamically stable	Symptomatic, unstable angina and/or acute myocardial infarction, cardiac enzymes abnormal, hemodynamically stable	Symptomatic, unstable angina and/or acute myocardial infarction, cardiac enzymes abnormal, hemodynamically unstable	Death		
		•	dium secondary to coronary artery	disease. The clinical presentation	covers a		
	unstable angina to myocardial infa		I		I		
Aortic valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis by imaging	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death		
Definition: A disorder characteriz	ed by a defect in aortic valve func	tion or structure.	T	T			
Asystole	Periods of asystole; non-urgent medical management indicated	-	-	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteriz	ed by a dysrhythmia without cardi	ac electrical activity. Typically, this	is accompanied by cessation of the	ne pumping function of the heart.			
Atrial fibrillation	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker), or ablation	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteriz originates above the ventricles.	ed by a dysrhythmia without disce	rnible P waves and an irregular ve	entricular response due to multiple	reentry circuits. The rhythm distur	bance		
Atrial flutter	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker), or ablation	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteriz atria.	ed by a dysrhythmia with organize	ed rhythmic atrial contractions with	a rate of 200-300 beats per minut	e. The rhythm disturbance origina	tes in the		
Atrioventricular block complete	-	Non-urgent intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteriz	ed by a dysrhythmia with complete	e failure of atrial electrical impulse	conduction through the AV node t	to the ventricles.			
Atrioventricular block first degree	Asymptomatic, intervention not indicated	Non-urgent intervention indicated	-	-	-		
	ed by a dysrhythmia with a delay interval greater than 200 milliseco	·	tion of an electrical impulse throug	gh the atrioventricular (AV) node b	eyond 0.		
Cardiac arrest	-	-	-	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteriz	ed by cessation of the pumping fu	nction of the heart.					
Chest pain - cardiac	Mild pain	Moderate pain; limiting instrumental ADL	Pain at rest; limiting self care ADL	-	-		
Definition: A disorder characteriz	ed by substernal discomfort due to	o insufficient myocardial oxygenati	on.				
Conduction disorder	Mild symptoms; intervention not indicated	Moderate symptoms	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteriz	ed by pathological irregularities in	the cardiac conduction system.	T				
Constrictive pericarditis	-	-	Symptomatic heart failure or other cardiac symptoms, responsive to intervention	Refractory heart failure or other poorly controlled cardiac symptoms	Death		
	1	1	1 .	1	e action.		
Definition: A disorder characteriz	ed by a thickened and fibrotic peri	cardial sac; these fibrotic changes	impede normai myocardiai iunciid	on by restricting myocardial musch			

		Cardiac disord	ers		
Grade					
Adverse Event	1	2	3	4	5
Left ventricular systolic dysfunction	-	-	Symptomatic due to drop in ejection fraction responsive to intervention	Refractory or poorly controlled heart failure due to drop in ejection fraction; intervention such as ventricular assist device, intravenous vasopressor support, or heart transplant indicated	Death
	zed by failure of the left ventricle to nea, orthopnea, and other signs ar		e an increase in distending pressur	e and in end-diastolic volume. Clin	ical
Mitral valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis by imaging	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death
Definition: A disorder characteriz	red by a defect in mitral valve func	tion or structure.		T	T
Mobitz (type) II atrioventricular block	Asymptomatic, intervention not indicated	Symptomatic; medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening consequences; urgent intervention indicated	Death
	zed by a dysrhythmia with relatively atrioventricular (AV) node to the ve	•	block of an atrial impulse. This is t	he result of intermittent failure of a	trial electri
Mobitz type I	Asymptomatic, intervention not indicated	Symptomatic; medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening consequences; urgent intervention indicated	Death
	red by a dysrhythmia with a progre on through the atrioventricular (AV		rior to the blocking of an atrial impu	Ilse. This is the result of intermitter	nt failure o
Myocardial infarction	-	Asymptomatic and cardiac enzymes minimally abnormal and no evidence of ischemic ECG changes	Severe symptoms; cardiac enzymes abnormal; hemodynamically stable; ECG changes consistent with infarction	Life-threatening consequences; hemodynamically unstable	Death
Definition: A disorder characteriz	red by gross necrosis of the myoca	ardium; this is due to an interruption	on of blood supply to the area.		•
Myocarditis	Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	Death
Definition: A disorder characteriz	ed by inflammation of the muscle	tissue of the heart.			
Palpitations	Mild symptoms; intervention not indicated	Intervention indicated	-	-	-
Definition: A disorder characteriz	red by an unpleasant sensation of	irregular and/or forceful beating o	f the heart.		
Paroxysmal atrial tachycardia	Asymptomatic, intervention not indicated	Symptomatic; medical management indicated	IV medication indicated	Life-threatening consequences; incompletely controlled medically; cardioversion indicated	Death
Definition: A disorder characteriz originates in the atria.	red by a dysrhythmia with abrupt o	nset and sudden termination of a	trial contractions with a rate of 150-	-250 beats per minute. The rhythm	n disturbar
Pericardial effusion	-	Asymptomatic effusion size small to moderate	Effusion with physiologic consequences	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	red by fluid collection within the pe	ricardial sac, usually due to inflan	nmation.		
Pericardial tamponade	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
	ed by an increase in intrapericardi	al pressure due to the collection	of blood or fluid in the pericardium.	T	1
Definition: A disorder characteriz					
Definition: A disorder characteriz Pericarditis	Asymptomatic, ECG or physical findings (e.g., rub) consistent with pericarditis	Symptomatic pericarditis (e.g., chest pain)	Pericarditis with physiologic consequences (e.g., pericardial constriction)	Life-threatening consequences; urgent intervention indicated	Death

	Cardiac disorders							
			Grade					
Adverse Event	1	2	3	4	5			
Pulmonary valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis by imaging	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death			
Definition: A disorder characteriz	ed by a defect in pulmonary valve	function or structure.	i	i	1			
Restrictive cardiomyopathy	-	-	Symptomatic heart failure or other cardiac symptoms, responsive to intervention	Refractory heart failure or other poorly controlled cardiac symptoms	Death			
	ed by an inability of the ventricles				I			
Right ventricular dysfunction	Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Severe symptoms, associated with hypoxemia, right heart failure; oxygen indicated	Life-threatening consequences; urgent intervention indicated (e.g., ventricular assist device); heart transplant indicated	Death			
Definition: A disorder characteriz	ed by impairment of right ventricul	ar function associated with low eje	ection fraction and a decrease in n	notility of the right ventricular wall.	1			
Sick sinus syndrome	Asymptomatic, intervention not indicated	Non-urgent intervention indicated	Severe, medically significant; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
	ed by a dysrhythmia with alternation			1	ı			
Sinus bradycardia	Asymptomatic, intervention not indicated	Symptomatic, medical intervention indicated	Severe, medically significant, medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteriz	ed by a dysrhythmia with a heart r	ate less than 60 beats per minute	that originates in the sinus node.					
Sinus tachycardia	Asymptomatic, intervention not indicated	Symptomatic; non-urgent medical intervention indicated	Urgent medical intervention indicated	-	-			
Definition: A disorder characteriz	ed by a dysrhythmia with a heart r	ate greater than 100 beats per mi	nute that originates in the sinus no	ode.	1			
Supraventricular tachycardia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteriz	ed by a dysrhythmia with a heart r	ate greater than 100 beats per mi	nute that originates above the ven	tricles.				
Tricuspid valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death			
	ed by a defect in tricuspid valve fu							
Ventricular arrhythmia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death			
Definition: A disorder characteriz	ed by a dysrhythmia that originate	s in the ventricles.	T	T				
Ventricular fibrillation	-	-	-	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death			
Definition: A disorder characteriz ventricles.	ed by a dysrhythmia without disce	rnible QRS complexes due to rapi	d repetitive excitation of myocardi	al fibers without coordinated contra	action of the			
Ventricular tachycardia	-	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death			
Definition: A disorder characteriz	ed by a dysrhythmia with a heart r	ate greater than 100 beats per mi	nute that originates distal to the bu	indle of His.				
Wolff-Parkinson-White syndrome	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with procedure	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteriz	ed by the presence of an accessor	ry conductive pathway between th	e atria and the ventricles that caus	ses premature ventricular activatio	n.			
Cardiac disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death			

Congenital, familial and genetic disorders							
		Grade					
Adverse Event	1	2	3	4	5		
Congenital, familial and genetic	Asymptomatic or mild	Moderate; minimal, local or	Severe or medically significant	Life-threatening consequences;	Death		
disorders - Other, specify	symptoms; clinical or diagnostic	noninvasive intervention	but not immediately life-	urgent intervention indicated			
	observations only; intervention	indicated; limiting age-	threatening; hospitalization or				
	not indicated	appropriate instrumental ADL	prolongation of existing				
			hospitalization indicated;				
i			disabling; limiting self care ADL				

Ear and labyrinth disorders							
Grade							
Adverse Event	1	2	3	4	5		
Ear pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-		
Definition: A disorder characteriz	red by a sensation of marked disco	mfort in the ear.	1				
External ear inflammation	External otitis with erythema or dry desquamation	External otitis with moist desquamation, edema, enhanced cerumen or discharge; tympanic membrane perforation; tympanostomy	External otitis with mastoiditis; stenosis or osteomyelitis; necrosis of soft tissue or bone	Urgent operative intervention indicated	Death		
Definition: A disorder characteriz	ed by inflammation, swelling and r	edness to the outer ear and ear ca	anal.				
External ear pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-		
Definition: A disorder characteriz	zed by a sensation of marked disco	mfort in the external ear region.					
Hearing impaired	Adults enrolled on a Monitoring Program (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift of 15 - 25 dB averaged at 2 contiguous test frequencies in at least one ear. Adults not enrolled in Monitoring Program: subjective change in hearing in the absence of documented hearing loss. Pediatric (on a 1, 2, 3, 4, 6 and	Adults enrolled in Monitoring Program (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift of >25 dB averaged at 2 contiguous test frequencies in at least one ear. Adults not enrolled in Monitoring Program: hearing loss but hearing aid or intervention not indicated; limiting instrumental ADL.	Adults enrolled in Monitoring Program (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift of >25 dB averaged at 3 contiguous test frequencies in at least one ear; therapeutic intervention indicated. Adults not enrolled in Monitoring Program: hearing loss with hearing aid or intervention indicated; limiting self care ADL.	Adults: Decrease in hearing to profound bilateral loss (absolute threshold >80 dB HL at 2 kHz and above); non-servicable hearing. Pediatric: Audiologic indication for cochlear implant and additional speech-language related services indicated.	-		
	8 kHz audiogram): Threshold shift >20 dB at 8 kHz in at least one ear.	Pediatric (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift >20 dB at 4 kHz and above in at least one ear.	Pediatric (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): hearing loss sufficient to indicate therapeutic intervention, including hearing aids; threshold shift >20 dB at 3 kHz and above in at least one ear; additional speech-language related services indicated.				
Definition: A disorder characteriz	ed by partial or complete loss of th	e ability to detect or understand s	ounds resulting from damage to e	ar structures.			
Middle ear inflammation Definition: A disorder characteriz	Serous otitis ted by inflammation (physiologic re	Serous otitis, medical intervention indicated sponse to irritation), swelling and	Mastoiditis; necrosis of canal soft tissue or bone redness to the middle ear.	Life-threatening consequences; urgent intervention indicated	Death		
Tinnitus	Mild symptoms; intervention not indicated		Severe symptoms; limiting self care ADL	-	-		
Definition: A disorder characterize	red by noise in the ears, such as ri	nging, buzzing, roaring or clicking.	1				
Vertigo	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-		
Definition: A disorder characteriz vertigo).	red by a sensation as if the externa	al world were revolving around the	patient (objective vertigo) or as if	he himself were revolving in space	(subjectiv		
Vestibular disorder	-	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-		
Definition: A disorder characteriz	red by dizziness, imbalance, nause	ea, and vision problems.	I				
Ear and labyrinth disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death		

Endocrine disorders							
			Grade				
Adverse Event	1	2	3	4	5		
Adrenal insufficiency	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death		
	rs when the adrenal cortex does not ison's disease or primary adrenal in:	· -	cortisol and in some cases, the ho	ormone aldosterone. It may be due	to a disorde		
Cushingoid	Mild symptoms; intervention not indicated		Severe symptoms, medical intervention or hospitalization indicated	-	-		
Definition: A disorder character osteoporosis, usually due to ex	rized by signs and symptoms that re cogenous corticosteroids.	semble Cushing's disease or synd	drome: buffalo hump obesity, striat	tions, adiposity, hypertension, diab	etes, and		
Delayed puberty	-	No breast development by age 13 yrs for females; testes volume of <3 cc or no Tanner Stage 2 development by age 14.5 yrs for males	No breast development by age 14 yrs for females; no increase in testes volume or no Tanner Stage 2 by age 16 yrs for males; hormone replacement indicated	-	-		
Definition: A disorder character	rized by unusually late sexual maturi	ity.					
Growth accelerated	-	>= +2 SD (standard deviation) above mid parental height or target height	-	-	-		
Definition: A disorder character	rized by greater growth than expecte	ed for age.	1				
Hyperparathyroidism	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-		
Definition: A disorder character the blood).	rized by an increase in production of	parathyroid hormone by the para	thyroid glands. This results in hypo	ercalcemia (abnormally high levels	of calcium i		
Hyperthyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder character	rized by excessive levels of thyroid h	normone in the body. Common ca	uses include an overactive thyroid	gland or thyroid hormone overdos	se.		
Hypoparathyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; medical intervention or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder character	rized by a decrease in production of	parathyroid hormone by the parat	hyroid glands.	•	•		
Hypothyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid replacement indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death		
	rized by a decrease in production of		and.	1	1		
Precocious puberty	Physical signs of puberty with no biochemical markers for females <8 years and males <9 years	Physical signs and biochemical markers of puberty for females <8 years and males <9 years	-	-	-		
Definition: A disorder character 9 for boys.	rized by unusually early developmen	nt of secondary sexual features; th	e onset of sexual maturation begir	ns usually before age 8 for girls an	d before age		
Virilization	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-		
Definition: A disorder character	rized by inappropriate masculinization	on occurring in a female or prepub	ertal male.				
Endocrine disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death		

Intervention indicated (e.g., topical agents); limiting vision (worse than poical agents); limiting instrumental ADL Definition: A disorder characterized by an area of epithelial tissue loss on the surface of the cornea. It is associated with inflammatory cells in the cornea and anterior chamber. Dry eye Asymptomatic; clinical or diagnostic observations only; mild symptoms relieved by lubricants Definition: A disorder characterized by dryness of the cornea and conjunctiva. Extraocular muscle paresis Asymptomatic; clinical or diagnostic observations only instrumental ADL Definition: A disorder characterized by incomplete paralysis of an extraocular muscle. Eye pain Mild pain Symptomatic; clinical or diagnostic observations only; intervention disorder Asymptomatic; clinical or diagnostic observations only; intervention not indicated by instrumental ADL Definition: A disorder characterized by impaired eyelid function. Eyelid function disorder characterized by impaired eyelid function. Elashing lights Symptomatic but not limiting ADL Definition: A disorder characterized by a sudden or brief burst of light. Elicitors: A disorder characterized by a notividual seeing spots before their eyes. The spots are shadows of opaque cell fragments in the vitreous humor or lens.			Eye di	sorders					
Elevent vision is intervention not indicated and provided vision in transcentrized by visual perception of unclear or fuzzy inages. Symptomatic conductated decrease in visual activity of the crystalline let not of decrease in visual activity of the crystalline let not of decrease in visual activity of the crystalline let not of decrease in visual activity of the crystalline let not of decrease in visual activity of the crystalline let not of the eye. Definition: A disorder characterized by partial or complete opacity of the crystalline let not of one or totol eyes. This results in a decrease in visual activity and eventual blindhess if intervention indicated (e.g., or intervention indicated (e.g., artibudos), intervention indicated (e.g., because in personal properties in the created (e.g., artibudos), intervention indicated (e.g., because in visual activity and eventual blindhess if intervention indicated (e.g., because in visual activity and eventual blindhess if intervention indicated (e.g., because in visual activity and eventual blindhess if intervention indicated (e.g., because in visual activity and eventual blindhess if intervention indicated (e.g., artibudos), intervention ind		Grade							
Definition: A disorder characterized by visual perception of undersor for fazy irranges. Definition: A disorder characterized by visual perception of undersor fazy irranges. Definition: A disorder characterized by visual perception of undersor fazy irranges. Definition: A disorder characterized by partial or complete opacity of the crystalline fens of one or both eyes. This results in a decrease in visual acuity and eventual bilindness if any according to the complete opacity of the crystalline fens of one or both eyes. This results in a decrease in visual acuity and eventual bilindness if any according to the complete opacity of the crystalline fens of one or both eyes. This results in a decrease in visual acuity and eventual bilindness if any according to the complete opacity of the crystalline fens of one or both eyes. This results in a decrease in visual acuity and eventual bilindness if according to the complete opacity with a complete opacity of the crystalline fens of one or both eyes. This results in a decrease in visual acuity and eventual bilindness if according to the complete opacity with a complete opacity of the crystalline fens of one or both eyes. This results in a decrease in visual acuity and eventual bilindness if according to the complete opacity of the crystalline fens of one or both eyes. This results in a decrease in visual acuity and eventual bilindness if according to the complete opacity with a complete opacity of the crystalline fens of one or both eyes. This results in a decrease in visual acuity and eventual bilindness if according to the complete opacity with a complete opacity	Adverse Event	1	2	3	4	5			
Asymptomatic: clinical or disponents control			instrumental ADL	Limiting self care ADL	-	-			
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symptoms: intervention not indicated (e.g. ambibotics); limiting and referees to the conjunctives of the eye. Symptomatic, medical intervention indicated (e.g. topical spans); limiting self care ADL; electining vision (worse than 2040 but better than 2020) our worse) in the object of spansor of the symptomatic, clinical or diagnostic observations only; alors trained and intervention indicated (e.g. topical spans); limiting self care ADL; electining vision (worse than 2040 but better than 2020) our worse) in the object spansor indicated from the surface of the connea. It is associated with inflammatory cells in the cornea and anterior chamber. Derivation Derivation		terized by partial or complete op	pacity of the crystalline lens of o	one or both eyes. This results in	n a decrease in visual acuity an	d eventual blindness if			
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diagnostic observations only; Individual seeing special function. A disorder characterized by dryress of the comea and conjunctiva. Extraocular muscle pareisis Asymptomatic; clinical or diagnostic observations only; Individual seeing special function in dicated Symptomatic; clinical or diagnostic observations only; Individual seeing special special function. A disorder characterized by incomplete paralysis of an extraocular muscle. Eye pain Mild pain Moderate pain; limiting instrumental ADL Severe pain; limiting self care ADL; - - - - -	Definition: A disorder charac	terized by an area of epithelial ti	ssue loss on the surface of the	cornea. It is associated with in	flammatory cells in the cornea	and anterior chamber.			
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light blindness Symptomatic but not limiting Limiting instrumental ADL Limiting self care ADL Blindness (20/200 or worse)		-	Symptomatic; medical intervention indicated (e.g., topical agents); limiting	Decline in vision (worse than 20/40 but better than 20/200); limiting self care	Perforation or blindness (20/200 or worse) in the	-			
	Definition: A disorder charac	terized by inflammation to the co	ornea of the eye.						
	light blindness		Limiting instrumental ADL	Limiting self care ADL	, ,	-			

		Eye dis	sorders		
			Grade		
Adverse Event	1	2	3	4	5
Optic nerve disorder	Asymptomatic; clinical or diagnostic observations only	Limiting vision of the affected eye (20/40 or better)	eye (worse than 20/40 but better than 20/200)	Blindness (20/200 or worse) in the affected eye	-
	erized by involvement of the op	·	i		1
Papilledema	Asymptomatic; no visual field defects	vision; visual field defect present sparing the central 20 degrees	Marked visual field defect (worse than 20/40 but better than 20/200)	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder charact	erized by swelling around the o	ptic disc. T	<u> </u>	<u> </u>	
Photophobia	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder charact	erized by fear and avoidance of	f light.			
Retinal detachment	Asymptomatic	Exudative and visual acuity 20/40 or better	Rhegmatogenous or exudative detachment; operative intervention indicated; decline in vision (worse than 20/40 but better than 20/200)	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder charact	erized by the separation of the	inner retina layers from the und	derlying pigment epithelium.		
Retinal tear	-	Laser therapy or pneumopexy indicated	Vitroretinal surgical repair indicated	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder charact	erized by a small laceration of t	he retina, this occurs when the	vitreous separates from the re	tina. Symptoms include flashes	s and floaters.
Retinal vascular disorder	-	Topical medication indicated	Intravitreal medication; operative intervention indicated	-	-
Definition: A disorder charact	erized by pathological retinal bl	ood vessels that adversely affe	cts vision.		
Retinopathy	Asymptomatic; clinical or diagnostic observations only	Symptomatic with moderate decrease in visual acuity (20/40 or better); limiting instrumental ADL	Symptomatic with marked decrease in visual acuity (worse than 20/40); disabling; limiting self care ADL	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder involvin	g the retina.				
Scleral disorder	Asymptomatic; clinical or diagnostic observations only	Symptomatic, limiting instrumental ADL; moderate decrease in visual acuity (20/40 or better)	Symptomatic, limiting self care ADL; marked decrease in visual acuity (worse than 20/40)	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder charact	erized by involvement of the sc	lera of the eye.	T	T	1
Uveitis	Asymptomatic; clinical or diagnostic observations only	•	Posterior or pan-uveitis	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder charact	erized by inflammation to the uv	vea of the eye.	1	Ι	ı
Vitreous hemorrhage	Asymptomatic or mild symptoms; clinical or diagnostic observations only	Symptomatic; limiting instrumental ADL	Limiting self care ADL; vitrectomy indicated	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder charact	erized by blood extravasation in	nto the vitreous humor.	T	T	T
Watering eyes	Intervention not indicated	Intervention indicated	Operative intervention indicated	-	-
Definition: A disorder of excess	ssive tearing in the eyes; it can	be caused by overproduction of	of tears or impaired drainage of	the tear duct.	
Eye disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately sight- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care	Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye	-

		Gastrointestinal dis	orders		
			Grade		
Adverse Event	1	2	3	4	5
Abdominal distension	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe discomfort; limiting self care ADL	-	-
Definition: A disorder characte	erized by swelling of the abdomen.				1
Abdominal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characte	erized by a sensation of marked disco	omfort in the abdominal region.	r	Г	1
Anal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	erized by an abnormal communication	between the opening in the anal	canal to the perianal skin.		
Anal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	erized by bleeding from the anal region	on.	T		1
Anal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	erized by inflammation of the mucous	membrane of the anus.	I		
Anal necrosis	-	- in the engl region	TPN or hospitalization indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
	erized by a necrotic process occurring		Cavara nain, limiting calf care		
Anal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
	erized by a sensation of marked disco		0 , , , ,	Let up a control of the control of t	Б. "
Anal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Symptomatic and severely altered GI function; non- emergent operative intervention indicated; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characte	erized by a narrowing of the lumen of	the anal canal.			
Anal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characte	erized by a circumscribed, inflammato	ory and necrotic erosive lesion on t	he mucosal surface of the anal ca	nal.	
Ascites	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characte	erized by accumulation of serous or h	emorrhagic fluid in the peritoneal	cavity.	•	•
Bloating	No change in bowel function or oral intake	Symptomatic, decreased oral intake; change in bowel function	-	-	-
Definition: A disorder characte	rized by subject-reported feeling of ι	-	men.	•	•
Cecal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	erized by bleeding from the cecum.			•	•
Cheilitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; intervention indicated	-	-
		1	I .	ı	I

Gastrointestinal disorders Grade								
		Ι .			l .			
Adverse Event	1	2	3	4				
Colitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characte	rized by inflammation of the colon.							
Colonic fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; bowel rest, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characte	rized by an abnormal communication	between the large intestine and	another organ or anatomic site.					
Colonic hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characte	rized by bleeding from the colon.	T	T	Γ	1			
Colonic obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated rized by blockage of the normal flow	Symptomatic; altered GI function	Hospitalization indicated; elective operative intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death			
	Tized by blockage of the normal flow				D41-			
Colonic perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
	rized by a rupture in the colonic wall.				1			
Colonic stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characte	rized by a narrowing of the lumen of	the colon.	'	'				
Colonic ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characte	rized by a circumscribed, inflammato	ory and necrotic erosive lesion on	the mucosal surface of the colon.					
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL	Obstipation with manual evacuation indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characte	rized by irregular and infrequent or d	ifficult evacuation of the bowels.						
Dental caries	One or more dental caries, not involving the root	Dental caries involving the root	Dental caries resulting in pulpitis or periapical abscess or resulting in tooth loss	-	-			
Definition: A disorder characte	rized by the decay of a tooth, in whice	th it becomes softened, discolored	and/or porous.					
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characte	rized by frequent and watery bowel r	movements.						
Dry mouth	Symptomatic (e.g., dry or thick	Moderate symptoms; oral intake	Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva <0.1 ml/min	-	-			

	Gastrointestinal disorders							
			Grade	1				
Adverse Event	1	2	3	4	5			
Duodenal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characte	erized by an abnormal communication	n between the duodenum and and	other organ or anatomic site.					
Duodenal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characte	erized by bleeding from the duodenur	n.						
Duodenal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Hospitalization or elective operative intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characte	erized by blockage of the normal flow	of stomach contents through the	duodenum.					
Duodenal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characte	erized by a rupture in the duodenal w	all.	 	1	1			
Duodenal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characte	erized by a narrowing of the lumen of	the duodenum.						
Duodenal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characte	erized by a circumscribed, inflammato	ory and necrotic erosive lesion on	the mucosal surface of the duoder	nal wall.				
Dyspepsia	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; surgical intervention indicated	-	-			
	erized by an uncomfortable, often pai	nful feeling in the stomach, resulti	ing from impaired digestion. Sympt	oms include burning stomach, blo	ating,			
heartburn, nausea and vomiti Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing	Severely altered eating/swallowing; tube feeding or TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characte	erized by difficulty in swallowing.	1	'	1				
Enterocolitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe or persistent abdominal pain; fever; ileus; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characte	erized by inflammation of the small ar	nd large intestines.		1				
Enterovesical fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; noninvasive intervention indicated	Severe, medically significant; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characte	erized by an abnormal communication	n between the urinary bladder and	d the intestine.					
Esophageal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characte	erized by an abnormal communication	n between the esophagus and and	other organ or anatomic site.					
Esophageal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical	Transfusion, radiologic,	Life-threatening consequences;	Death			

Gastrointestinal disorders								
	Grade							
Adverse Event	1	2	3	4	5			
Esophageal necrosis	-	-	Inability to aliment adequately by GI tract; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characte	erized by a necrotic process occurring	g in the esophageal wall.						
Esophageal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characte	erized by blockage of the normal flow	of the contents in the esophagus	T	T				
Esophageal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characte	rized by a sensation of marked disco	omfort in the esophageal region.						
Esophageal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
	erized by a rupture in the wall of the e	1	1	<u> </u>				
Esophageal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characte	rized by a narrowing of the lumen of	the esophagus.		·				
Esophageal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characte	erized by a circumscribed, inflammate	ory and necrotic erosive lesion on	the mucosal surface of the esopha	geal wall.				
Esophageal varices hemorrhage	-	Self-limited; intervention not indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characte	rized by bleeding from esophageal v	varices.						
Esophagitis Definition: A disorder characte	Asymptomatic; clinical or diagnostic observations only; intervention not indicated erized by inflammation of the esophar	Symptomatic; altered eating/swallowing; oral supplements indicated	Severely altered eating/swallowing; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Fecal incontinence	Occasional use of pads required		Sovere aymptome: elective					
			Severe symptoms; elective operative intervention indicated	-				
	erized by inability to control the escap							
Flatulence	Mild symptoms; intervention not indicated	psychosocial sequelae	-	-	-			
Definition: A disorder characte	erized by a state of excessive gas in			Ι				
Gastric fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; bowel rest; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characte	erized by an abnormal communication	n between the stomach and anoth	ner organ or anatomic site.	T				
Gastric hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characte	erized by bleeding from the gastric wa	all.	1	1				
Gastric necrosis	-	-	Inability to aliment adequately by GI tract; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
	T.	I		1	1			

		Gastrointestinal dis	orders						
Grade									
Adverse Event	1	2	3	4	5				
Gastric perforation Definition: A disorder characterize	- zed by a rupture in the stomach wa	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death				
Gastric stenosis	Asymptomatic; clinical or	Symptomatic; altered GI	Severely altered GI function;	Life-threatening consequences;	Death				
Gastic stellosis	diagnostic observations only; intervention not indicated	function	tube feeding; hospitalization indicated; elective operative intervention indicated	urgent operative intervention indicated	Death				
Definition: A disorder characterize	zed by a narrowing of the lumen of	the stomach.	T	T					
Gastric ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death				
Definition: A disorder characteriz	zed by a circumscribed, inflammato	ory and necrotic erosive lesion on t		h. T					
Gastritis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated	Severely altered eating or gastric function; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death				
Definition: A disorder characterize	zed by inflammation of the stomach	1. T	T	T	1				
Gastroesophageal reflux disease	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; surgical intervention indicated	-	-				
	zed by reflux of the gastric and/or d result in injury to the esophageal m			nd usually caused by incompetend	ce of the lowe				
Gastrointestinal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death				
Definition: A disorder characteriz	zed by an abnormal communication	n between any part of the gastroin	testinal system and another organ	or anatomic site.					
Gastrointestinal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-				
Definition: A disorder characterize	zed by a sensation of marked disco	mfort in the gastrointestinal region	i.	•					
Gastroparesis	Mild nausea, early satiety and bloating, able to maintain caloric intake on regular diet	Moderate symptoms; able to	Weight loss; refractory to medical intervention; unable to maintain nutrition orally	-	-				
Definition: A disorder characterize	zed by an incomplete paralysis of the	he muscles of the stomach wall re	sulting in delayed emptying of the	gastric contents into the small into	estine.				
Gingival pain	Mild pain	Moderate pain interfering with oral intake	Severe pain; inability to aliment orally	-	-				
Definition: A disorder characterize	zed by a sensation of marked disco	omfort in the gingival region.	T	T	T				
Hemorrhoidal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death				
Definition: A disorder characterize	zed by bleeding from the hemorrho	ids.	T	T					
Hemorrhoids	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; banding or medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	-	-				
Definition: A disorder characterize	zed by the presence of dilated vein	s in the rectum and surrounding a	rea.	ı					
lleal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death				
Definition: A disorder characterize	zed by an abnormal communication	between the ileum and another o	organ or anatomic site.						
lleal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death				
Definition: A disorder characteria	zed by bleeding from the ileal wall.								

Gastrointestinal disorders								
			Grade					
Adverse Event	1	2	3	4	5			
leal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characterize	zed by blockage of the normal flow	of the intestinal contents in the ile	eum.	1				
leal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characteriz	zed by a rupture in the ileal wall.			T				
leal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characteriz	zed by a narrowing of the lumen of	the ileum.	T	T	1			
lleal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characteriz	zed by a circumscribed, inflammato	ory and necrotic erosive lesion on	the mucosal surface of the ileum.	1				
lleus	- zed by failure of the ileum to transp	Symptomatic; altered GI function; bowel rest indicated	Severely altered GI function; TPN indicated	Life-threatening consequences; urgent intervention indicated	Death			
Intra-abdominal hemorrhage	_	Medical intervention or minor	Transfusion, radiologic,	Life-threatening consequences;	Death			
ntia-abuoniinai nemormage		cauterization indicated	endoscopic, or elective operative intervention indicated	urgent intervention indicated	Death			
Definition: A disorder characteriz	zed by bleeding in the abdominal c	avity.	T	T				
Jejunal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characterize	' zed by an abnormal communication	n between the jejunum and anoth	er organ or anatomic site.	'				
Jejunal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteriz	zed by bleeding from the jejunal wa	all.	•	•	•			
Jejunal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characteriz	zed by blockage of the normal flow	of the intestinal contents in the je	ejunum.					
Jejunal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characteriz	। zed by a rupture in the jejunal wall.	•		•	•			
Jejunal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characteriz	zed by a narrowing of the lumen of	the jejunum.						
Jejunal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characteriz	zed by a circumscribed, inflammato	ory and necrotic erosive lesion on	the mucosal surface of the jejunun	1.				
ip pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			

	<u> </u>	Gastrointestinal dis			
			Grade		1
Adverse Event	1	2	3	4	5
Lower gastrointestinal nemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder character	rized by bleeding from the lower gas	trointestinal tract (small intestine,	large intestine, and anus).	T	
Malabsorption	-	Altered diet; oral intervention indicated	Inability to aliment adequately; TPN indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder character	rized by inadequate absorption of nu	trients in the small intestine. Sym	ptoms include abdominal marked o	discomfort, bloating and diarrhea.	
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder character	rized by inflammation of the oral mu	cosal.	1	T	
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-
Definition: A disorder character	rized by a queasy sensation and/or t	the urge to vomit.		<u> </u>	
Obstruction gastric	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder character	rized by blockage of the normal flow	of the contents in the stomach.	1	T	
Oral cavity fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder character	rized by an abnormal communication	between the oral cavity and ano	ther organ or anatomic site.	,	
Oral dysesthesia	Mild discomfort; not interfering with oral intake	Moderate pain; interfering with oral intake	Disabling pain; tube feeding or TPN indicated	-	-
Definition: A disorder character	rized by a burning or tingling sensati	on on the lips, tongue or entire mo	outh.	T	1
Oral hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder character	rized by bleeding from the mouth.				
Oral pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder character	rized by a sensation of marked disco	omfort in the mouth, tongue or lips		1	
Pancreatic duct stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder character	rized by a narrowing of the lumen of	the pancreatic duct.			
Pancreatic fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder character	rized by an abnormal communication	·	ner organ or anatomic site.	<u> </u>	
Pancreatic hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder character	rized by bleeding from the pancreas	T	T	T	
Pancreatic necrosis	-	-	Tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder character	rized by a necrotic process occurring	in the pancreas.			
Pancreatitis	-	Enzyme elevation or radiologic findings only	Severe pain; vomiting; medical intervention indicated (e.g., analgesia, nutritional support)	Life-threatening consequences; urgent intervention indicated	Death

Gastrointestinal disorders								
			Grade					
Adverse Event	1	2	3	4	5			
efinition: A disorder characte	rized by inflammation of the pancrea	S.		I				
Periodontal disease	Gingival recession or gingivitis; limited bleeding on probing; mild local bone loss	Moderate gingival recession or gingivitis; multiple sites of bleeding on probing; moderate bone loss	Spontaneous bleeding; severe bone loss with or without tooth loss; osteonecrosis of maxilla or mandible	-	-			
	ngival tissue around the teeth.				1			
eritoneal necrosis	-	-	Tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characte	rized by a necrotic process occurring	in the peritoneum.		T	1			
Proctitis	Rectal discomfort, intervention not indicated	Symptoms (e.g., rectal discomfort, passing blood or mucus); medical intervention indicated; limiting instrumental ADL	Severe symptoms; fecal urgency or stool incontinence; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characte	rized by inflammation of the rectum.							
Rectal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characte	rized by an abnormal communication	n between the rectum and another	r organ or anatomic site.					
Rectal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characte	rized by bleeding from the rectal wall	and discharged from the anus.						
Rectal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characte	rized by inflammation of the mucous	membrane of the rectum.						
Rectal necrosis	-	-	Tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characte	rized by a necrotic process occurring	in the rectal wall.		T				
Rectal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characte	rized by blockage of the normal flow	of the intestinal contents in the re		Т	1			
Rectal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
	rized by a sensation of marked disco	1	I_	I	_			
Rectal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characte	rized by a rupture in the rectal wall.							
Rectal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characte	rized by a narrowing of the lumen of	the rectum.						
Rectal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function (e.g. altered dietary habits, vomiting, diarrhea)	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death			

		Gastrointestinal dis	Grade		
Adverse Event	1	2	Grade 3		5
Adverse Event	1			4	
Retroperitoneal hemorrhage	-	Self-limited; intervention indicated	Transfusion, medical, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteri:	zed by bleeding from the retroperite	oneal area.	T		
Salivary duct inflammation	Slightly thickened saliva; slightly altered taste (e.g., metallic)	Thick, ropy, sticky saliva; markedly altered taste; alteration in diet indicated; secretion-induced symptoms; limiting instrumental ADL	Acute salivary gland necrosis; severe secretion-induced symptoms (e.g., thick saliva/oral secretions or gagging); tube feeding or TPN indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteria	zed by inflammation of the salivary	duct.			_
Salivary gland fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; tube feeding indicated	Severely altered GI function; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteri:	zed by an abnormal communication	between a salivary gland and an	other organ or anatomic site.		
Small intestinal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe pain; interfering with oral intake; tube feeding, TPN or hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteri:	zed by inflammation of the mucous	membrane of the small intestine.			
Small intestinal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteriz	zed by blockage of the normal flow	of the intestinal contents.			
Small intestinal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteri	zed by a rupture in the small intesti	ne wall.			
Small intestinal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Symptomatic and severely altered GI function; tube feeding, TPN or hospitalization indicated; non-emergent operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteria	zed by a narrowing of the lumen of	the small intestine.			
Small intestine ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteri	zed by a circumscribed, inflammato	ory and necrotic erosive lesion on	the mucosal surface of the small in	itestine.	
Stomach pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterize	zed by a sensation of marked disco	omfort in the stomach.	1	I	
Tooth development disorder	Asymptomatic; hypoplasia of tooth or enamel	Impairment correctable with oral surgery	Maldevelopment with impairment not surgically correctable; disabling	-	-
Definition: A disorder characteri:	zed by a pathological process of th	e teeth occurring during tooth dev	elopment.	Γ	
Footh discoloration	Surface stains	-	-	-	-
Definition: A disorder characteri:	zed by a change in tooth hue or tin	t.			
oothache	Mild pain	Moderate pain; limiting	Severe pain; limiting self care	-	

		Gastrointestinal dis	orders					
Grade								
Adverse Event	1	2	3	4	5			
Typhlitis	-	-	Symptomatic (e.g., abdominal pain, fever, change in bowel habits with ileus); peritoneal signs	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characteriz	ed by inflammation of the cecum.							
Upper gastrointestinal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteriz	ed by bleeding from the upper gas	trointestinal tract (oral cavity, pha	rynx, esophagus, and stomach).					
Vomiting	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	>=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteriz	ed by the reflexive act of ejecting t	he contents of the stomach throug	gh the mouth.					
Gastrointestinal disorders - Other, specify	, , ,	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death			

Grade								
Adverse Event	1	2	3	4	5			
Chills	Mild sensation of cold; shivering; chattering of teeth	Moderate tremor of the entire body; narcotics indicated	Severe or prolonged, not responsive to narcotics	-	-			
Definition: A disorder chara	cterized by a sensation of cold that ofte	n marks a physiologic response to	sweating after a fever.					
Death neonatal	-	-	-	-	Death			
Definition: A disorder chara	cterized by cessation of life occurring d	uring the first 28 days of life.	•	•	•			
Death NOS	-	-	-	-	Death			
Definition: A cessation of life	e that cannot be attributed to a CTCAE	term associated with Grade 5.						
Edema face	Localized facial edema	Moderate localized facial edema; limiting instrumental ADL	Severe swelling; limiting self care ADL	-	-			
Definition: A disorder chara	cterized by swelling due to excessive flu	uid accumulation in facial tissues.	1		_			
Edema limbs	5 - 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection	>10 - 30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL	>30% inter-limb discrepancy in volume; gross deviation from normal anatomic contour; limiting self care ADL	-	-			
Definition: A disorder chara	cterized by swelling due to excessive flu	uid accumulation in the upper or lo	wer extremities.		•			
Edema trunk	Swelling or obscuration of anatomic architecture on close inspection	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL	Gross deviation from normal anatomic contour; limiting self care ADL	-	-			
Definition: A disorder chara	cterized by swelling due to excessive flu	uid accumulation in the trunk area			_			
Facial pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder chara	cterized by a sensation of marked disco	omfort in the face.						
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL	-	-			
Definition: A disorder chara	cterized by a state of generalized weak	ness with a pronounced inability to	summon sufficient energy to acc	omplish daily activities.	_			
Fever	38.0 - 39.0 degrees C (100.4 - 102.2 degrees F)	>39.0 - 40.0 degrees C (102.3 - 104.0 degrees F)	>40.0 degrees C (>104.0 degrees F) for <=24 hrs	>40.0 degrees C (>104.0 degrees F) for >24 hrs	Death			
Definition: A disorder chara	cterized by elevation of the body's temp	perature above the upper limit of n	ormal.	1	1			
Flu like symptoms	Mild flu-like symptoms present	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-			
Definition: A disorder charac cough.	cterized by a group of symptoms simila	r to those observed in patients wit	h the flu. It includes fever, chills, b	ody aches, malaise, loss of appeti	ite and dr			
Gait disturbance	Mild change in gait (e.g., wide- based, limping or hobbling)	Moderate change in gait (e.g., wide-based, limping or hobbling); assistive device indicated; limiting instrumental ADL	Disabling; limiting self care ADL	-	-			
Definition: A disorder charac	cterized by walking difficulties.	1	•	•	•			
Hypothermia	-	35 - >32 degrees C; 95 - >89.6 degrees F	32 - >28 degrees C; 89.6 - >82.4 degrees F	<=28 degrees C; 82.4 degrees F; life-threatening consequences (e.g., coma, hypotension, pulmonary edema,	Death			

Grade							
Adverse Event	1	2	3	4	5		
nfusion related reaction	Mild transient reaction; infusion	Therapy or infusion interruption	Prolonged (e.g., not rapidly	Life-threatening consequences;	Death		
illiusion relateu reaction	interruption not indicated;	indicated but responds promptly	responsive to symptomatic	urgent intervention indicated	Dealli		
	intervention not indicated	to symptomatic treatment (e.g.,	medication and/or brief	argoni intervention indicated			
	intervention net indicated	antihistamines, NSAIDS,	interruption of infusion);				
		narcotics, IV fluids); prophylactic					
		medications indicated for <=24	following initial improvement;				
		hrs	hospitalization indicated for				
			clinical sequelae				
Definition: A disorder characteriz	ा zed by adverse reaction to the infus	ı sion of pharmacological or biologic		I	1		
nfusion site extravasation	T-	Erythema with associated	Ulceration or necrosis; severe	Life-threatening consequences;	Death		
		symptoms (e.g., edema, pain,	tissue damage; operative	urgent intervention indicated			
		induration, phlebitis)	intervention indicated				
Definition: A disorder characteriz	zed by leakage of a pharmacologic	or a biologic substance from the i	nfusion site into the surrounding ti	r ssue. Signs and symptoms include	। e induratio		
	sation and marked discomfort at the	•		д,			
njection site reaction	Tenderness with or without	Pain; lipodystrophy; edema;	Ulceration or necrosis; severe	Life-threatening consequences;	Death		
	associated symptoms (e.g.,	phlebitis	tissue damage; operative	urgent intervention indicated			
	warmth, erythema, itching)		intervention indicated				
Definition: A disorder characteriz	zed by an intense adverse reaction	(usually immunologic) developing	at the site of an injection.	•	•		
rritability	Mild; easily consolable	Moderate; limiting instrumental	Severe abnormal or excessive	-	-		
,		ADL; increased attention	response; limiting self care ADL;				
		indicated	inconsolable				
Definition: A disorder characteriz	zed by an abnormal responsivenes	ı s to stimuli or physiological arousa	l may be in response to pain frid	i ht a drug an emotional situation o	า or a medio		
condition.	.ou by an abnormal responsiveness	o to difficili of physiological arouse	ai, may be in reopened to pain, mg	nt, a arag, an omotional olication	or a moan		
Localized edema	Localized to dependent areas,	Moderate localized edema and	Severe localized edema and	-	-		
	no disability or functional	intervention indicated; limiting	intervention indicated; limiting				
	impairment	instrumental ADL	self care ADL				
Definition: A disorder characterize	red by swelling due to excessive flu	ı	1	ı	1		
Malaise	Uneasiness or lack of well being		_	_	l _		
		being; limiting instrumental ADL					
Definition: A disorder characteriz	zed by a feeling of general discomf	ort or uneasiness, an out-of-sorts	feeling.				
Multi-organ failure] -	-	Shock with azotemia and acid-	Life-threatening consequences	Death		
3			base disturbances; significant	(e.g., vasopressor dependent			
			coagulation abnormalities	and oliguric or anuric or			
				ischemic colitis or lactic			
				acidosis)			
Definition: A disorder characteriz	ed by progressive deterioration of	the lungs, liver, kidney and clotting	mechanisms.	acidosis)			
	zed by progressive deterioration of			acidosis)	 -		
	Asymptomatic localized neck	Moderate neck edema; slight	Generalized neck edema (e.g.,	acidosis)	 -		
		Moderate neck edema; slight obliteration of anatomic	Generalized neck edema (e.g., difficulty in turning neck);	-	-		
	Asymptomatic localized neck	Moderate neck edema; slight	Generalized neck edema (e.g.,	-	-		
Neck edema	Asymptomatic localized neck	Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL	Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL	-	-		
Neck edema Definition: A disorder characteriz	Asymptomatic localized neck edema	Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL	Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL	-	-		
Neck edema Definition: A disorder characteriz	Asymptomatic localized neck edema	Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL stion of excessive fluid in the neck	Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL	-	-		
Neck edema Definition: A disorder characteriz Non-cardiac chest pain	Asymptomatic localized neck edema	Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL stion of excessive fluid in the neck Moderate pain; limiting instrumental ADL	Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL Severe pain; limiting self care	acidosis)	-		
Neck edema Definition: A disorder characteriz Non-cardiac chest pain	Asymptomatic localized neck edema received by swelling due to an accumula Mild pain	Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL stion of excessive fluid in the neck Moderate pain; limiting instrumental ADL	Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL Severe pain; limiting self care	acidosis)	-		
Neck edema Definition: A disorder characteriz Non-cardiac chest pain Definition: A disorder characteriz	Asymptomatic localized neck edema zed by swelling due to an accumula Mild pain	Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL ation of excessive fluid in the neck Moderate pain; limiting instrumental ADL lated to a heart disorder.	Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL Severe pain; limiting self care ADL	acidosis) - -	-		
Neck edema Definition: A disorder characteriz Non-cardiac chest pain Definition: A disorder characteriz Pain	Asymptomatic localized neck edema zed by swelling due to an accumula Mild pain	Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL ation of excessive fluid in the neck Moderate pain; limiting instrumental ADL lated to a heart disorder. Moderate pain; limiting instrumental ADL	Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL Severe pain; limiting self care ADL Severe pain; limiting self care	-	-		
Neck edema Definition: A disorder characteriz Non-cardiac chest pain Definition: A disorder characteriz Pain Definition: A disorder characteriz	Asymptomatic localized neck edema zed by swelling due to an accumulated by discomfort in the chest unrelessed by discomfort in the chest unreless	Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL ation of excessive fluid in the neck Moderate pain; limiting instrumental ADL lated to a heart disorder. Moderate pain; limiting instrumental ADL	Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL Severe pain; limiting self care ADL Severe pain; limiting self care		Death		
Definition: A disorder characterization-cardiac chest pain Definition: A disorder characterization Definition: A disorder characterization	Asymptomatic localized neck edema zed by swelling due to an accumulated by discomfort in the chest unrelessed by discomfort in the chest unreless	Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL ation of excessive fluid in the neck Moderate pain; limiting instrumental ADL lated to a heart disorder. Moderate pain; limiting instrumental ADL comfort, distress or agony.	Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL Severe pain; limiting self care ADL Severe pain; limiting self care ADL	-	Death		
Definition: A disorder characteriz Non-cardiac chest pain Definition: A disorder characteriz Pain Definition: A disorder characteriz Sudden death NOS	Asymptomatic localized neck edema zed by swelling due to an accumular Mild pain zed by discomfort in the chest unrel Mild pain zed by the sensation of marked discontinuous control of mark	Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL ation of excessive fluid in the neck Moderate pain; limiting instrumental ADL lated to a heart disorder. Moderate pain; limiting instrumental ADL comfort, distress or agony.	Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL Severe pain; limiting self care ADL Severe pain; limiting self care ADL	-	Death		
Definition: A disorder characterize Non-cardiac chest pain Definition: A disorder characterize Pain Definition: A disorder characterize Sudden death NOS Definition: An unexpected cessa General disorders and	Asymptomatic localized neck edema ged by swelling due to an accumular Mild pain ged by discomfort in the chest unrel Mild pain ged by the sensation of marked discomplete that cannot be attributed Asymptomatic or mild	Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL stion of excessive fluid in the neck Moderate pain; limiting instrumental ADL lated to a heart disorder. Moderate pain; limiting instrumental ADL comfort, distress or agony.	Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL Severe pain; limiting self care ADL Severe pain; limiting self care ADL	-	<u>'</u>		
Definition: A disorder characterize Non-cardiac chest pain Definition: A disorder characterize Pain Definition: A disorder characterize Sudden death NOS Definition: An unexpected cessa General disorders and administration site conditions -	Asymptomatic localized neck edema red by swelling due to an accumular Mild pain red by discomfort in the chest unrel Mild pain red by the sensation of marked discrete by t	Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL ation of excessive fluid in the neck Moderate pain; limiting instrumental ADL lated to a heart disorder. Moderate pain; limiting instrumental ADL comfort, distress or agony. - to a CTCAE term associated with Moderate; minimal, local or noninvasive intervention	Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL Severe pain; limiting self care ADL Severe pain; limiting self care ADL - a Grade 5. Severe or medically significant but not immediately life-	- Life-threatening consequences;	<u>'</u>		
Neck edema Definition: A disorder characteriz Non-cardiac chest pain Definition: A disorder characteriz Pain Definition: A disorder characteriz Sudden death NOS	Asymptomatic localized neck edema ged by swelling due to an accumular will pain ged by discomfort in the chest unrel will pain ged by the sensation of marked discretion of life that cannot be attributed asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention	Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL ation of excessive fluid in the neck Moderate pain; limiting instrumental ADL lated to a heart disorder. Moderate pain; limiting instrumental ADL comfort, distress or agony. - to a CTCAE term associated with Moderate; minimal, local or noninvasive intervention indicated; limiting age-	Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL Severe pain; limiting self care ADL Severe pain; limiting self care ADL - a Grade 5. Severe or medically significant but not immediately lifethreatening; hospitalization or	- Life-threatening consequences;	<u>'</u>		
Definition: A disorder characterize Non-cardiac chest pain Definition: A disorder characterize Pain Definition: A disorder characterize Sudden death NOS Definition: An unexpected cessa General disorders and administration site conditions -	Asymptomatic localized neck edema red by swelling due to an accumular Mild pain red by discomfort in the chest unrel Mild pain red by the sensation of marked discrete by t	Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL ation of excessive fluid in the neck Moderate pain; limiting instrumental ADL lated to a heart disorder. Moderate pain; limiting instrumental ADL comfort, distress or agony. - to a CTCAE term associated with Moderate; minimal, local or noninvasive intervention	Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL Severe pain; limiting self care ADL Severe pain; limiting self care ADL - a Grade 5. Severe or medically significant but not immediately life-	- Life-threatening consequences;	<u>'</u>		

diagnostic observations only; intervention not indicated with the particular development of the bits duct. Biliary fishing	Hepatobiliary disorders								
Bille duck stenosis disproaches conservations more indicated or depression deservations more indicated or pression in indicated conservations more indicated or pression indicated or conservation indicated indicated or conservation indicated or conservation indicated or conservation indicated indicated or conservation indicated indicated or conservation indicated indicated or conservation indicated indicat				1		Ι -			
diagnostic observations only. intervention not indicated in the second process. It is a second process									
Definition: A disorder characterized by an abnormal communication between the bile ducks and another organ or anatomic alte. Cholecystitis - Symptomatic, medical intervention indicated intervention indica	Bile duct stenosis	diagnostic observations only;	function; IV fluids indicated <24	radiologic, endoscopic or elective operative intervention	urgent operative intervention	Death			
Definition: A disorder characterized by an abnormal communication between the bile ducts and another organ or anatomic site. Chole-cystilis - Symptomatic, medical intervention indicated intervention indicated intervention indicated. Definition: A disorder characterized by inflammation involving the gallbladder. It may be associated with the presence of gallstones. Gallbladder finatula Asymptomatic clinical or dispositic observations only, intervention indicated or disp	Definition: A disorder character	rized by a narrowing of the lumen of	the bile duct.		1	1			
Symptomatic medical minvention indicated methodologic, endoscopic of electrice operative intervention indicated methodologic methodologic minvention indicated methodologic	Biliary fistula	-	1 1 1	TPN indicated; endoscopic intervention indicated; elective	urgent operative intervention	Death			
Intervention indicated intervention indicated endoscopic or elective operative intervention indicated intervention indicated indicated with the presence of gallationes. Asymptomatic clinical or diagnostic observations only, intervention not indicated diagnostic observations only, intervention not indicated with the presence of gallationes. Symptomatic or severely affected of function. The Indicated, radiologic, endoscopic or elective operative intervention indicated indicated or elective operative intervention indicated indicated or elective operative intervention indicated indicated or elective operative indicated or elective operative indicated indicated or elective operative indicated indicated or elective operative indicated indicated or operative indicated or oper	Definition: A disorder character	rized by an abnormal communication	n between the bile ducts and anoth	ner organ or anatomic site.					
Gallbladder fistula Asymptomatic clinical or diagnostic observations only; intervention not indicated Definition: A disorder characterized by an abnormal communication between the gallbladder and another organ or anatomic site. Gallbladder necrosis Life-threatening consequences; Uncetton, Indicated Definition: A disorder characterized by an entrolic process occurring in the gallbladder and another organ or anatomic site. Gallbladder necrosis Life-threatening consequences; Ungent operative intervention indicated Definition: A disorder characterized by a necrolic process occurring in the gallbladder. Gallbladder obstruction Asymptomatic; clinical or diagnostic observations only; intervention not indicated Definition: A disorder characterized by blockage of the normal flow of the contents of the gallbladder. Gallbladder pain Mild pain Mild pain Moderate pain; limiting pair care John A disorder characterized by a sensation of marked discomfort in the gallbladder region. Gallbladder perforation Life-threatening consequences; Ungent operative intervention indicated Definition: A disorder characterized by a sensation of marked discomfort in the gallbladder. Gallbladder pain Mild pain Moderate pain; limiting self care A disorder characterized by a rupture in the gallbladder wall. Hepatic failure Asterixis; mild encephalopathy; Implementation indicated Definition: A disorder characterized by the inability of the liver to metabolize chemicals in the body. Laboratory test results reveal abnormal plasma levels of ammonia, bilirubin, lace delivity organiase, and alkaline phosphatase. Hepatic necrosis Life-threatening consequences; Ungent intervention indicated Definition: A disorder characterized by bleeding from the liver. Hepatic necrosis Life-threatening consequences; Ungent indicated Life-threatening consequences; Ungent indicated Life-threatening consequences; Ungent indicated Life-threatening consequences; Ungent indicated Life-threatening	Cholecystitis	-		endoscopic or elective operative	urgent operative intervention	Death			
diagnostic observations only, intervention not indicated Cf. function; TPN indicated; radiologic, endoscopic or elective operative intervention indicated Definition: A disorder characterized by an abnormal communication between the galibladder and another organ or anatomic site. Galibladder necrosis -	Definition: A disorder character	rized by inflammation involving the g	jallbladder. It may be associated w	vith the presence of gallstones.	'				
Galibladder necrosis	Gallbladder fistula	diagnostic observations only;	7 '	GI function; TPN indicated; radiologic, endoscopic or elective operative intervention	urgent operative intervention	Death			
Definition: A disorder characterized by a necrotic process occurring in the gallbladder. Gallbladder obstruction Asymptomatic; clinical or diagnostic observations only; intervention not indicated Asymptomatic; difficultion; by fluids indicated discolor, in the gallbladder. Symptomatic and severely altered GI function; tube feeding. TPN or hospitalization indicated; non-emergent operative intervention indicated indicated; non-emergent operative intervention indicated. Gallbladder pain Mild pain Moderate pain; limiting pain; severe pain; limiting self care ADL Definition: A disorder characterized by a sensation of marked discomfort in the gallbladder region. Gallbladder perforation - Life-threatening consequences; urgent intervention indicated urgent indivention indicated	Definition: A disorder character	rized by an abnormal communication	n between the gallbladder and and	other organ or anatomic site.		1			
Asymptomatic; clinical or diagnostic observations only; intervention not indicated severally intervention indicated severally indicated severally intervention indicated severally indicated	Gallbladder necrosis	-	-	-	urgent radiologic or operative	Death			
diagnostic observations only; intervention not indicated hrs surprise intervention not indicated with the service intervention indicated indicated in the service intervention indicated i	Definition: A disorder character	rized by a necrotic process occurring	g in the gallbladder.						
Gallbladder pain Mild pain Moderate pain; limiting instrumental ADL ADL Definition: A disorder characterized by a sensation of marked discomfort in the gallbladder region. Gallbladder perforation Life-threatening consequences; urgent intervention indicated urgent indicated urg		diagnostic observations only; intervention not indicated	function; IV fluids indicated <24 hrs	altered GI function; tube feeding, TPN or hospitalization indicated; non-emergent operative intervention indicated	urgent operative intervention	Death			
Definition: A disorder characterized by a sensation of marked discomfort in the gallbladder region. Gallbladder perforation Life-threatening consequences; urgent intervention indicated Definition: A disorder characterized by a rupture in the gallbladder wall. Hepatic failure Asterixis; mild encephalopathy; limiting self care ADL life-threatening consequences encephalopathy; coma; life-threatening consequences encephalopathy; coma; life-threatening consequences have threatening consequences. It is the patic failure encephalopathy is provided by the inability of the liver to metabolize chemicals in the body. Laboratory test results reveal abnormal plasma levels of ammonia, billirubin, lace dehydrogenase, and alkaline phosphatase. Hepatic hemorrhage Mild; intervention not indicated intervention indicat						1			
Definition: A disorder characterized by a rupture in the gallbladder wall. Hepatic failure - Asterixis; mild encephalopathy; limiting self care ADL life-threatening consequences; urgent intervention indicated Death disorder characterized by the inability of the liver to metabolize chemicals in the body. Laboratory test results reveal abnormal plasma levels of ammonia, bilirubin, lace dehydrogenase, and alkaline phosphatase. Hepatic hemorrhage Mild; intervention not indicated intervention indicated intervention indicated Definition: A disorder characterized by bleeding from the liver. Hepatic necrosis Life-threatening consequences; urgent intervention indicated Definition: A disorder characterized by a necrotic process occurring in the hepatic parenchyma. Hepatic pain Mild pain Moderate to severe encephalopathy; coma; life-threatening consequences; urgent intervention indicated Life-threatening consequences; urgent intervention indicated Life-threatening consequences; urgent intervention indicated Definition: A disorder characterized by a necrotic process occurring in the hepatic parenchyma. Hepatic pain Mild pain Moderate pain; limiting Severe pain; limiting self care ADL Life-threatening consequences; urgent radiologic or operative intervention indicated Radiologic, endoscopic or elective operative intervention Life-threatening consequences; urgent radiologic on operative intervention undicated Radiologic, endoscopic or elective operative intervention Life-threatening consequences; urgent operative intervention undicated Radiologic, endoscopic or elective operative intervention	Gallbladder pain	Mild pain			-	-			
Definition: A disorder characterized by a rupture in the gallbladder wall. Hepatic failure - Asterixis; mild encephalopathy; limiting self care ADL imiting self care ADL imiting consequences Definition: A disorder characterized by the inability of the liver to metabolize chemicals in the body. Laboratory test results reveal abnormal plasma levels of ammonia, bilirubin, lac dehydrogenase, and alkaline phosphatase. Hepatic hemorrhage Mild; intervention not indicated Symptomatic; medical intervention indicated Definition: A disorder characterized by bleeding from the liver. Hepatic necrosis - Iffe-threatening consequences; urgent intervention indicated Definition: A disorder characterized by a necrotic process occurring in the hepatic parenchyma. Hepatic pain Mild pain Moderate pain; limiting self care ADL Effective operative intervention Life-threatening consequences; urgent radiologic or operative intervention indicated Definition: A disorder characterized by a necrotic process occurring in the hepatic parenchyma. Perforation bile duct - Radiologic, endoscopic or elective operative intervention Life-threatening consequences; urgent radiologic or operative intervention - Radiologic, endoscopic or elective operative intervention	Definition: A disorder character	rized by a sensation of marked disco	omfort in the gallbladder region.						
Hepatic failure - Asterixis; mild encephalopathy; limiting self care ADL - Asterixis; mild encephalopathy; limiting self care ADL - Asterixis; mild encephalopathy; limiting self care ADL - Asterixis; mild encephalopathy; coma; life-threatening consequences Definition: A disorder characterized by the inability of the liver to metabolize chemicals in the body. Laboratory test results reveal abnormal plasma levels of ammonia, bilirubin, lac dehydrogenase, and alkaline phosphatase. Hepatic hemorrhage Mild; intervention not indicated Symptomatic; medical intervention indicated Symptomatic; medical intervention indicated Definition: A disorder characterized by bleeding from the liver. Hepatic necrosis Life-threatening consequences; urgent radiologic or operative intervention indicated Definition: A disorder characterized by a necrotic process occurring in the hepatic parenchyma. Hepatic pain Mild pain Moderate pain; limiting Severe pain; limiting instrumental ADL Definition: A disorder characterized by a sensation of marked discomfort in the liver region. Perforation bile duct - Radiologic, endoscopic or elective operative intervention Life-threatening consequences; Death Life-threatening consequences; Death - Radiologic, endoscopic or elective operative intervention	Gallbladder perforation	-	-	-		Death			
Definition: A disorder characterized by the inability of the liver to metabolize chemicals in the body. Laboratory test results reveal abnormal plasma levels of ammonia, bilirubin, lac dehydrogenase, and alkaline phosphatase. Hepatic hemorrhage Mild; intervention not indicated Symptomatic; medical intervention indicated intervention indicate	Definition: A disorder character	rized by a rupture in the gallbladder	wall.		-				
dehydrogenase, and alkaline phosphatase. Hepatic hemorrhage Mild; intervention not indicated Intervention Indicated	Hepatic failure	-	-	limiting self care ADL	encephalopathy; coma; life-	Death			
Hepatic hemorrhage Mild; intervention not indicated symptomatic; medical intervention indicated wirgent radiologic or operative intervention indicated wirgent parenchyma. Hepatic pain Mild pain Moderate pain; limiting instrumental ADL Severe pain; limiting self care ADL Definition: A disorder characterized by a sensation of marked discomfort in the liver region. Perforation bile duct - Radiologic, endoscopic or elective operative intervention wirgent operative intervention wirge			etabolize chemicals in the body. L	aboratory test results reveal abnor	mal plasma levels of ammonia, bi	lirubin, lac			
Hepatic necrosis - Life-threatening consequences; urgent radiologic or operative intervention indicated Definition: A disorder characterized by a necrotic process occurring in the hepatic parenchyma. Hepatic pain Mild pain Moderate pain; limiting instrumental ADL Definition: A disorder characterized by a sensation of marked discomfort in the liver region. Perforation bile duct - Radiologic, endoscopic or elective operative intervention Life-threatening consequences; urgent operative intervention Death - Peath - Death			2 2	Transfusion indicated		Death			
Definition: A disorder characterized by a necrotic process occurring in the hepatic parenchyma. Hepatic pain Mild pain Moderate pain; limiting instrumental ADL Severe pain; limiting self care ADL Definition: A disorder characterized by a sensation of marked discomfort in the liver region. Perforation bile duct - Radiologic, endoscopic or elective operative intervention urgent operative intervention	Definition: A disorder character	rized by bleeding from the liver.							
Hepatic pain Mild pain Moderate pain; limiting severe pain; limiting self care ADL Definition: A disorder characterized by a sensation of marked discomfort in the liver region. Perforation bile duct - Radiologic, endoscopic or elective operative intervention Life-threatening consequences; urgent operative intervention	Hepatic necrosis	-	-	-	urgent radiologic or operative	Death			
instrumental ADL ADL Definition: A disorder characterized by a sensation of marked discomfort in the liver region. Perforation bile duct - Radiologic, endoscopic or elective operative intervention urgent operative intervention Death	Definition: A disorder character	rized by a necrotic process occurring	g in the hepatic parenchyma.						
Perforation bile duct - Radiologic, endoscopic or elective operative intervention Life-threatening consequences; urgent operative intervention	Hepatic pain	Mild pain	, ,		-	-			
elective operative intervention urgent operative intervention	Definition: A disorder character	rized by a sensation of marked disco	omfort in the liver region.	_					
	Perforation bile duct	-	-	elective operative intervention	urgent operative intervention	Death			

		Hepatobiliary diso	rders					
	Grade							
Adverse Event	1	2	3	4	5			
Portal hypertension	-	Decreased portal vein flow	Reversal/retrograde portal vein flow; associated with varices and/or ascites	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characterize	ed by an increase in blood pressu	re in the portal venous system.						
Portal vein thrombosis	-	Intervention not indicated	Medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characterize	ed by the formation of a thrombus	(blood clot) in the portal vein.						
Hepatobiliary disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated;	Life-threatening consequences; urgent intervention indicated	Death			
			disabling; limiting self care ADL					

		Immune system dis	orders		
			Grade		
Adverse Event	1	2	3	4	5
Allergic reaction Definition: A disorder characteria	Transient flushing or rash, drug fever <38 degrees C (<100.4 degrees F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
Anaphylaxis	- zed by an acute inflammatory react	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
mmune response. Clinically, it p	resents with breathing difficulty, diz	zziness, hypotension, cyanosis an	d loss of consciousness and may	lead to death.	
Autoimmune disorder	Asymptomatic; serologic or other evidence of autoimmune reaction, with normal organ function; intervention not indicated	Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism)	Autoimmune reactions involving major organ (e.g., colitis, anemia, myocarditis, kidney)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder resulting fr tissue constituents.	om loss of function or tissue destru	ction of an organ or multiple orga	ns, arising from humoral or cellula	r immune responses of the individe	ual to his ow
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilatory support indicated	Death
Definition: A disorder characterize	zed by nausea, headache, tachyca	rdia, hypotension, rash, and shorti	ness of breath; it is caused by the	release of cytokines from the cells	i.
Serum sickness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate arthralgia; fever, rash, urticaria, antihistamines indicated	extensive rash; steroids or IV fluids indicated	Life-threatening consequences; pressor or ventilatory support indicated	Death
	zed by a delayed-type hypersensitive foreign antigen. Symptoms include				
Immune system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

		Infections and infes	tations		
			Grade		
Adverse Event	1	2	3	4	5
Abdominal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	rized by an infectious process invo	lving the abdominal cavity.		1	
Anorectal infection	Localized; local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	rized by an infectious process invo	lving the anal area and the rectum.	IV antibiotic antifungal or	Life threatening consequences:	Death
Appendicitis			IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Deam
	rized by acute inflammation to the		1		Б. "
Appendicitis perforated	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	rized by acute inflammation to the iceal wall rupture causes the releas	vermiform appendix caused by a pa	athogenic agent with gangrenous o	changes resulting in the rupture of	the
Arteritis infective	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	rized by an infectious process invo	lving an artery.		· 	
Biliary tract infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	rized by an infectious process invo	lving the biliary tract.	1	ı	ı
Bladder infection	-	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	rized by an infectious process invo	lving the bladder.			•
Bone infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	rized by an infectious process invol		T	1.	
Breast infection	-	Local infection with moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	Severe infection; axillary adenitis; IV antibacterial, antifungal, or antiviral intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	rized by an infectious process invol	1		1.	
Bronchial infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	rized by an infectious process invol	lving the bronchi.		1	1
Catheter related infection	-	Localized; local intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	rized by an infectious process that	arises secondary to catheter use.			
Cecal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

		Infections and infes	Grade		
Adverse Event	1	2	3	4	5
	ed by an infectious process involv		, ,	7	
Cervicitis infection	ed by all infectious process involv	Localized; local intervention	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
Del vicius il liection	-	indicated (e.g., topical antibiotic,	antiviral intervention indicated;	urgent intervention indicated	Death
		antifungal, or antiviral)	radiologic or operative	g	
			intervention indicated		
Definition: A disorder characterize	ed by an infectious process involv	ing the uterine cervix.			
Conjunctivitis infective	-	Localized; local intervention	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
		indicated (e.g., topical antibiotic,	antiviral intervention indicated;	urgent intervention indicated	
		antifungal, or antiviral)	radiologic or operative		
		<u> </u>	intervention indicated		
	ed by an infectious process involv		1	<u> </u>	
Corneal infection	-	Localized; local intervention	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
		indicated (e.g., topical antibiotic, antifungal, or antiviral)	antiviral intervention indicated; radiologic or operative	urgent intervention indicated	
		a	intervention indicated		
Definition: A disorder characterize	। ed by an infectious process involv	ing the cornea.	1	1	1
Cranial nerve infection	-	-	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
			antiviral intervention indicated;	urgent intervention indicated	Dou
			radiologic or operative		
			intervention indicated		
Definition: A disorder characterize	ed by an infectious process involv	ing a cranial nerve.	T	1	
Device related infection	-	-	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
			antiviral intervention indicated;	urgent intervention indicated	
			radiologic or operative		
			intervention indicated	1	l
	ed by an infectious process involv	T		I	I
Duodenal infection	-	Moderate symptoms; medical	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
		intervention indicated (e.g., oral antibiotics)	antiviral intervention indicated; radiologic or operative	urgent intervention indicated	
			intervention indicated		
Definition: A disorder characterize	ed by an infectious process involv	ing the duodenum.	'	1	'
Encephalitis infection	-	-	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
			antiviral intervention indicated;	urgent intervention indicated	
			severe changes in mental		
			status; self-limited seizure		
			activity; focal neurologic		
5 6 W A P 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1			abnormalities		I
	ed by an infectious process involv	ing the brain tissue.	N/ El-1-El-1-El-1	l :f- thti	D"
Encephalomyelitis infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated;	Life-threatening consequences; urgent intervention indicated	Death
			radiologic or operative	argoni intervention mulcated	
			intervention indicated		
Definition: A disorder characterize	ed by an infectious process involv	ing the brain and spinal cord tissu	es.		
Endocarditis infective	-	-	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
			antiviral intervention indicated;	urgent intervention indicated	
			radiologic or operative		
			intervention indicated		
Definition: A disorder characterize	ed by an infectious process involv	ing the endocardial layer of the he	art.	1	
Endophthalmitis	-	Local intervention indicated	Systemic intervention or	Blindness (20/200 or worse)	-
- naopina anniao					

Grade							
Adverse Event	1	2	3	4	5		
Enterocolitis infectious	•	Passage of >3 unformed stools	IV antibiotic, antifungal, or	Life-threatening consequences;	Death		
-neroconus inicolous		per 24 hrs or duration of illness >48 hrs; moderate abdominal pain	antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated; profuse watery diarrhea with	urgent intervention indicated	Death		
Definition: A disparday share storic		ing the email and large intestines	signs of hypovolemia; bloody diarrhea; fever; severe abdominal pain; hospitalization indicated				
	zed by an infectious process involv	1			I		
Esophageal infection	-	Local intervention indicated (e.g., oral antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteriz	ed by an infectious process involv	ing the esophagus.	'	'	•		
Eye infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated; enucleation	Death		
Definition: A disorder characteriz	red by an infectious process involv	ing the eye.					
Gallbladder infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteriz	red by an infectious process involv	ing the gallbladder.	T	.			
Gum infection	Local therapy indicated (swish and swallow)	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteriz	red by an infectious process involv	ing the gums.	'	'	•		
Hepatic infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteriz	red by an infectious process involv	ing the liver.	ı	ı	•		
Hepatitis viral	Asymptomatic, treatment not indicated	-	Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis; reactivation of chronic hepatitis	Decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, coma)	Death		
Definition: A disorder characteriz	red by a viral pathologic process in	volving the liver parenchyma.					
nfective myositis	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteriz	red by an infectious process involv	ing the skeletal muscles.					
Joint infection	-	Localized; local intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); needle aspiration indicated (single or multiple)	Arthroscopic intervention indicated (e.g., drainage) or arthrotomy (e.g., open surgical drainage)	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteriz	। zed by an infectious process involv	1	ı	ı	1		
Kidney infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		

		Infections and infes						
		Grade						
Adverse Event	1	2	3	4	5			
Laryngitis	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder charac	terized by an inflammatory process	involving the larynx.						
Lip infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	-	-			
Definition: A disorder charac	terized by an infectious process invo	olving the lips.		· 				
Lung infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder charac	terized by an infectious process invo	olving the lungs.	1	T				
Lymph gland infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder charac	terized by an infectious process invo	olving the lymph nodes.	1					
Mediastinal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder charac	terized by an infectious process invo	olving the mediastinum.						
Meningitis	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated; focal neurologic deficit	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder charac	terized by acute inflammation of the	meninges of the brain and/or spinal	cord.	•	•			
Mucosal infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder charac	terized by an infectious process invo	olving a mucosal surface.						
Nail infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	-	-			
Definition: A disorder charac	terized by an infectious process invo	olving the nail.						
Otitis externa	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
		olving the outer ear and ear canal. C	•	ive water exposure (swimmer's ea	r infectio			
-	mptoms include fullness, itching, sw	velling and marked discomfort in the		I				
Otitis media	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder charac	terized by an infectious process invo	olving the middle ear.		1				
Ovarian infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			

		Infections and infes	tations		
			Grade		
Adverse Event	1	2	3	4	5
Pancreas infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	rized by an infectious process involv	ing the pancreas.		,	
Papulopustular rash	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; lifethreatening consequences	Death
	rized by an eruption consisting of pa				p, and upper
Paronychia	Nail fold edema or erythema; disruption of the cuticle	Localized intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	Surgical intervention or IV antibiotics indicated; limiting self care ADL	-	-
Definition: A disorder characte	rized by an infectious process involv	ing the soft tissues around the nai	l.	T	
Pelvic infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	rized by an infectious process involv				
Penile infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	rized by an infectious process involv	ing the penis.			_
Periorbital infection	rized by an infectious process involv	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Peripheral nerve infection	nized by an intectious process involv	Localized; local intervention	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
		indicated (e.g., topical antibiotic, antifungal, or antiviral)		urgent intervention indicated	beaut
	rized by an infectious process involv	ing the peripheral herves.	IV antihiotic antifun1	Life threatening con	Dooth
Peritoneal infection		-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	rized by an infectious process involv	ing the peritoneum.		Ī	
Pharyngitis	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	rized by inflammation of the throat.				
Phlebitis infective	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

y an infectious process involvin	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	Grade 3 s include erythema, marked disco IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated IV antibiotic, antifungal, or antiviral intervention indicated;	4 Infort, swelling, and induration alor Life-threatening consequences; urgent intervention indicated Life-threatening consequences;	5 ng the course
y an infectious process involving y an infectious process involving in y an infectious process involving y an infectious process involving	ng the vein. Clinical manifestation: Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral) ng the pleura. Moderate symptoms; oral intervention indicated (e.g.,	s include erythema, marked disco IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated IV antibiotic, antifungal, or	mfort, swelling, and induration alor Life-threatening consequences; urgent intervention indicated	ng the course
y an infectious process involvin	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral) ng the pleura. Moderate symptoms; oral intervention indicated (e.g.,	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated IV antibiotic, antifungal, or	Life-threatening consequences; urgent intervention indicated	·
y an infectious process involvir	indicated (e.g., topical antibiotic, antifungal, or antiviral) ng the pleura. Moderate symptoms; oral intervention indicated (e.g.,	antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated IV antibiotic, antifungal, or	urgent intervention indicated	Death
y an infectious process involvin	Moderate symptoms; oral intervention indicated (e.g.,		Life-threatening consequences:	
y an infectious process involvin	intervention indicated (e.g.,		II ite-threatening consequences:	- "
		radiologic, endoscopic, or operative intervention indicated	urgent intervention indicated	Death
lı	ng the prostate gland.			
i	indicated (e.g., topical antibiotic,	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	-	-
y a circumscribed and elevated	d skin lesion filled with pus.			
i	indicated (e.g., topical antibiotic,	-	-	-
y an infectious process involvin	ng the nasal mucosal.			
i	intervention indicated (e.g.,	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
y an infectious process involvin	ng the salivary gland.		•	
i	indicated (e.g., topical antibiotic,	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
y an infectious process involvin	ng the scrotum.			
	-	-	Life-threatening consequences; urgent intervention indicated	Death
y the presence of pathogenic n	nicroorganisms in the blood stream	m that cause a rapidly progressinຸ	g systemic reaction that may lead	to shock.
i	indicated (e.g., topical antibiotic,	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
y an infectious process involvin	ng the mucous membranes of the	paranasal sinuses.		
		IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
y an infectious process involvin	ng the skin.			
ļi	intervention indicated (e.g.,	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
y an infectious process involvin	ng the small intestine.			
	indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
y an intectious process involvin	ng soft tissues.			
	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
y y y y y	an infectious process involvir an infectious process involvir an infectious process involvir the presence of pathogenic n an infectious process involvir lized, local intervention ated an infectious process involvir	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral) an infectious process involving the mucous membranes of the lized, local intervention Oral intervention indicated (e.g.,	indicated (e.g., topical antibiotic, antifurngal, or antiviral) a circumscribed and elevated skin lesion filled with pus. Localized; local intervention indicated (e.g., antibiotic, antifungal, or antiviral) an infectious process involving the nasal mucosal. Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral) an infectious process involving the salivary gland. Localized; local intervention indicated (e.g., antibiotic, antifungal, or antiviral) an infectious process involving the salivary gland. Localized; local intervention indicated intervention indicated (e.g., topical antibiotic, antifungal, or antiviral) an infectious process involving the scrotum. Localized; local intervention indicated indicated (e.g., topical antibiotic, antifungal, or antiviral) Localized; local intervention indicated indiviral intervention indicated intervention indicated (e.g., antibiotic, antifungal, or antiviral intervention indicated	indicated (e.g., topical antibiotic, antifungal, or antiviral) a circumscribed and elevated skin lesion filled with pus. Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral) an infectious process involving the nasal mucosal. Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral) an infectious process involving the salivary gland. Localized; local intervention indicated (antifungal, or antiviral) Localized; local intervention indicated (antifungal, or antiviral) an infectious process involving the salivary gland. Localized; local intervention indicated (antifungal, or antiviral) an infectious process involving the scrotum. -

	1	Infections and infes	tations		
			Grade		
Adverse Event	1	2	3	4	5
Definition: A disorder characteriz	zed by an infectious process involving	ing the spleen.	T	1	
Stoma site infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	zed by an infectious process involvi	ing a stoma (surgically created op	ening on the surface of the body).		
Tooth infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	zed by an infectious process involvi	ing a tooth.			
Tracheitis	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	zed by an infectious process involving	ing the trachea.	T	T	1
Upper respiratory infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	zed by an infectious process involvi	ing the upper respiratory tract (nos	se, paranasal sinuses, pharynx, la	rynx, or trachea).	
Urethral infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	zed by an infectious process involvi	ing the urethra.			
Urinary tract infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	zed by an infectious process involvi	ing the urinary tract, most commo	nly the bladder and the urethra.		
Uterine infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	zed by an infectious process involvi	ing the endometrium. It may exten	d to the myometrium and parame	trial tissues.	
Vaginal infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	zed by an infectious process involvi	ing the vagina.		1	
Vulval infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	zed by an infectious process involvi	ing the vulva.			
Wound infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	zed by an infectious process involvi		<u> </u>	1	
Infections and infestations - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Injury, poisoning and procedural complications Grade								
Adverse Event	1	2	3	4	5			
Ankle fracture	Mild; non-surgical intervention	Limiting instrumental ADL;	Limiting self care ADL; elective	4	3			
	indicated	operative intervention indicated	surgery indicated		-			
Definition: A finding of damage affected leg and foot.	to the ankle joint characterized by a	a break in the continuity of the ank	le bone. Symptoms include marke	d discomfort, swelling and difficult	y moving the			
Aortic injury	-	_	Severe symptoms; limiting self	Life-threatening consequences;	Death			
. tortio injury			care ADL; disabling; repair or	evidence of end organ damage;	Dou			
			revision indicated	urgent operative intervention				
				indicated				
Definition: A finding of damage			1		1			
Arterial injury	Asymptomatic diagnostic	Symptomatic (e.g.,	Severe symptoms; limiting self	Life-threatening consequences;	Death			
	finding; intervention not indicated	claudication); repair or revision not indicated	care ADL; disabling; repair or revision indicated	evidence of end organ damage; urgent operative intervention				
	indicated	not indicated	Tevision indicated	indicated				
Definition: A finding of damage	to an artery.	'	'	'				
Biliary anastomotic leak	Asymptomatic diagnostic	Symptomatic; medical	Severe symptoms; radiologic,	Life-threatening consequences;	Death			
	observations only; intervention	intervention indicated	endoscopic or elective operative	urgent operative intervention				
	not indicated		intervention indicated	indicated				
Definition: A finding of leakage	of bile due to breakdown of a biliary	anastomosis (surgical connection	of two separate anatomic structu	res).	1			
Bladder anastomotic leak	Asymptomatic diagnostic	Symptomatic; medical	Severe symptoms; radiologic,	Life-threatening consequences;	Death			
	observations only; intervention	intervention indicated	endoscopic or elective operative	urgent operative intervention				
Definition: A finding of lookage	not indicated	 der apastomasis /surginal connec	intervention indicated	indicated	l			
Bruising	of urine due to breakdown of a blad	Generalized	LIOIT OF TWO SEPARATE ANATOMIC STRU	Liui es j.	_			
ruising	area	Generalized		-	-			
Definition: A finding of injury of	the soft tissues or bone characteriz	ed by leakage of blood into surrou	nding tissues.	'				
Burn	Minimal symptoms; intervention	Medical intervention; minimal	Moderate to major debridement	Life-threatening consequences	Death			
	not indicated	debridement indicated	or reconstruction indicated					
	integrity to the anatomic site of an			nicals, direct heat, electricity, flame	es and			
	e depends on the length and intensi							
Dermatitis radiation	Faint erythema or dry	Moderate to brisk erythema;	Moist desquamation in areas	Life-threatening consequences;	Death			
	desquamation	patchy moist desquamation, mostly confined to skin folds	other than skin folds and creases; bleeding induced by	skin necrosis or ulceration of full thickness dermis; spontaneous				
		and creases; moderate edema	minor trauma or abrasion	bleeding from involved site; skin				
		,		graft indicated				
Definition: A finding of cutaneo	us inflammatory reaction occurring	as a result of exposure to biological	ally effective levels of ionizing radia	ition.				
Esophageal anastomotic leak	Asymptomatic diagnostic	Symptomatic; medical	Severe symptoms; radiologic,	Life-threatening consequences;	Death			
	observations only; intervention	intervention indicated	endoscopic or elective operative	urgent operative intervention				
	not indicated		intervention indicated	indicated				
	due to breakdown of an esophagea			res).				
Fall	Minor with no resultant injuries; intervention not indicated	Symptomatic; noninvasive intervention indicated	Hospitalization indicated	-	-			
Definition: A finding of sudden	movement downward, usually result	1	I	l	l			
Fallopian tube anastomotic leal		Symptomatic; medical	Severe symptoms; radiologic,	Life-threatening consequences;	Death			
allopian tube anastomotic ical	diagnostic observations only;	intervention indicated	endoscopic or elective operative	i	Death			
	intervention not indicated		intervention indicated	indicated				
Definition: A finding of leakage	due to breakdown of a fallopian tub	e anastomosis (surgical connection	n of two separate anatomic structu	ıres).				
Fallopian tube perforation	Asymptomatic diagnostic	Symptomatic and intervention	Severe symptoms; elective	Life-threatening consequences;	Death			
	observations only; intervention	not indicated	operative intervention indicated	urgent operative intervention				
	not indicated		I	indicated (e.g., organ resection)	l			
Definition: A finding of rupture o					l			
Fracture	Asymptomatic; clinical or	Symptomatic but non-displaced;	Severe symptoms; displaced or	Life-threatening consequences;	Death			
	diagnostic observations only; intervention not indicated	immobilization indicated	open wound with bone exposure; disabling; operative	urgent intervention indicated				
	into vontion not indicated		intervention indicated					
	। c injury to the bone in which the cor	1	-	1	ı			

Injury, poisoning and procedural complications								
		T	Grade	Г				
Adverse Event	1	2	3	4	5			
Gastric anastomotic leak	Asymptomatic diagnostic	Symptomatic; medical	Severe symptoms; radiologic,	Life-threatening consequences;	Death			
	observations only; intervention not indicated	intervention indicated	endoscopic or elective operative intervention indicated	urgent operative intervention indicated				
Oofinition: A finding of lookage d	1	tomonia (aurainal connection of tw	•	maicated	1			
		tomosis (surgical connection of tw			I			
Gastrointestinal anastomotic eak	Asymptomatic diagnostic observations only; intervention	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative	Life-threatening consequences; urgent operative intervention	Death			
eak	not indicated	intervention indicated	intervention indicated	indicated				
Definition: A finding of lookage d	1	nal apartamania (aurainal cappan	•	1	I			
	ue to breakdown or a gastrollitesti		tion of two separate anatomic struc		Б. "			
Gastrointestinal stoma necrosis	-	Superficial necrosis;	Severe symptoms;	Life-threatening consequences;	Death			
		intervention not indicated	hospitalization or elective operative intervention indicated	urgent intervention indicated				
Definition: A finding of a pocretic	process occurring in the gostroint	antinal tract atoms	operative intervention indicated	I	I			
	process occurring in the gastroint							
Hip fracture	-	Hairline fracture; mild pain;	Severe pain; hospitalization or	Life-threatening consequences;	-			
		limiting instrumental ADL; non- surgical intervention indicated	intervention indicated for pain control (e.g., traction); operative	symptoms associated with neurovascular compromise				
		Surgical intervention indicated	intervention indicated	incurovascular compromise				
Definition: A finding of traumatic	I injury to the hin in which the contir	ı nuity of either the femoral head, fe	ा moral neck, intertrochanteric or su	I htrochanteric regions is broken	ı			
	lingary to ano mp in minor and demail	lany or oranor and remoral mode, re		1	Dooth			
Injury to carotid artery	-	-	Severe symptoms; limiting self care ADL (e.g., transient	Life-threatening consequences; urgent intervention indicated	Death			
			cerebral ischemia); repair or	argoni intorvention indicated				
			revision indicated					
Definition: A finding of damage to	the carotid artery.	ı	•	ı	•			
Injury to inferior vena cava		_	_	Life-threatening consequences;	Death			
injury to innonior rona oura				urgent intervention indicated	D Gui			
Definition: A finding of damage to	the inferior vena cava	I	1	1 9	U.			
Injury to jugular vein	_	_	Symptomatic limiting self care	Life-threatening consequences;	Death			
injury to jugular voiri			ADL; disabling; repair or	urgent intervention indicated	Death			
			revision indicated					
Definition: A finding of damage to	the iugular vein.	1	!	!	ı			
Injury to superior vena cava	Asymptomatic diagnostic	Symptomatic; repair or revision	Severe symptoms; limiting self	Life-threatening consequences;	Death			
injury to superior vena cava	finding; intervention not	not indicated	care ADL; disabling; repair or	evidence of end organ damage;	Death			
	indicated	The maidated	revision indicated	urgent operative intervention				
				indicated				
Definition: A finding of damage to	the superior vena cava.	Į.	•	ı	•			
Intestinal stoma leak	Asymptomatic diagnostic	Symptomatic; medical	Severe symptoms; radiologic,	Life-threatening consequences;	Death			
	observations only; intervention	intervention indicated	endoscopic or elective operative	urgent operative intervention				
	not indicated		intervention indicated	indicated				
Definition: A finding of leakage or	f contents from an intestinal stoma	' a (surgically created opening on th	e surface of the body).	•	•			
Intestinal stoma obstruction	-	Self-limited; intervention not	Severe symptoms; IV fluids,	Life-threatening consequences;	Death			
		indicated	tube feeding, or TPN indicated	urgent operative intervention				
			>=24 hrs; elective operative	indicated				
			intervention indicated					
Definition: A finding of blockage	of the normal flow of the contents	of the intestinal stoma.						
Intestinal stoma site bleeding	Minimal bleeding identified on	Moderate bleeding; medical	Severe bleeding; transfusion	Life-threatening consequences;	Death			
	clinical exam; intervention not	intervention indicated	indicated; radiologic or	urgent intervention indicated				
	indicated		endoscopic intervention					
			indicated					
Definition: A finding of blood leak	age from the intestinal stoma.	1	1					
Intraoperative arterial injury	Primary repair of injured	Partial resection of injured	Complete resection or	Life-threatening consequences;	Death			
	organ/structure indicated	organ/structure indicated	reconstruction of injured	urgent intervention indicated				
			organ/structure indicated;					
			disabling					
Definition: A finding of damage to	an artery during a surgical proce	dure.		I				
Intraoperative breast injury	Primary repair of injured	Partial resection of injured	Complete resection or	Life-threatening consequences;	Death			
	organ/structure indicated	organ/structure indicated	reconstruction of injured	urgent intervention indicated				
			organ/structure indicated;					
			disabling					

	,,	, poisoning and proced	Grade		
Adverse Event	1	2	3	4	5
	the breast parenchyma during a		•	-	
Intraoperative cardiac injury	-	-	Primary repair of injured organ/structure indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to	o the heart during a surgical proce	dure.			
Intraoperative ear injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection of injured organ/structure indicated; disabling (e.g., impaired hearing; impaired balance)	Life-threatening consequences; urgent intervention indicated	Death
	o the ear during a surgical procedu			T .	I
Intraoperative endocrine injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to	the endocrine gland during a sur	gical procedure.			
Intraoperative gastrointestinal injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to	the gastrointestinal system durin	g a surgical procedure.			
Intraoperative head and neck injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to	the head and neck during a surg	ical procedure.			
Intraoperative hemorrhage	-	-	Postoperative radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of uncontroll	ed bleeding during a surgical proc	edure.	ı	!	•
Intraoperative hepatobiliary injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to	the hepatic parenchyma and/or l	piliary tract during a surgical pro	cedure.		
Intraoperative musculoskeletal injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to	o the musculoskeletal system duri	ng a surgical procedure.		<u> </u>	
Intraoperative neurological injury	Primary repair of injured organ/structure indicated or the nervous system during a sur	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
			0 11 "		Б. "
Intraoperative ocular injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to	the eye during a surgical proced	ure.			
Intraoperative renal injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to	the kidney during a surgical prod	edure.			
Intraoperative reproductive tract injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated;	Life-threatening consequences; urgent intervention indicated	Death

Injury, poisoning and procedural complications Grade							
Adverse Event	1	2	3	4	5		
	the reproductive organs during a			·			
Intraoperative respiratory injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A finding of damage to	the respiratory system during a s	surgical procedure.					
Intraoperative skin injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A finding of damage to	the skin during a surgical proced	ure.					
Intraoperative splenic injury	the poleon during a cursical pre-	Primary repair of injured organ/structure indicated	Resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death		
	the spleen during a surgical proc		Complete resection or	Life threatening concernance	Death		
Intraoperative urinary injury Definition: A finding of damage to	Primary repair of injured organ/structure indicated the urinary system during a surg	Partial resection of injured organ/structure indicated	reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Deali		
Intraoperative venous injury	Primary repair of injured	Partial resection of injured	Complete resection or	Life-threatening consequences;	Death		
muaoperauve venous injury	organ/structure indicated	organ/structure indicated	reconstruction of injured organ/structure indicated; disabling	urgent intervention indicated	Deali		
Definition: A finding of damage to	a vein during a surgical procedu	re.	,				
Kidney anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A finding of leakage of	urine due to breakdown of a kidn	ey anastomosis (surgical connecti	on of two separate anatomic struc	tures).			
Large intestinal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A finding of leakage du	ue to breakdown of an anastomos	is (surgical connection of two sepa	arate anatomic structures) in the la	rge intestine.			
Pancreatic anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A finding of leakage du	· ·	nastomosis (surgical connection o	f two separate anatomic structure	s). I			
Pharyngeal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	indicated	Death		
			of two separate anatomic structure	ľ			
Postoperative hemorrhage	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; radiologic, endoscopic, or operative intervention indicated	Transfusion indicated of >=2 units (10 cc/kg for pediatrics) pRBCs beyond protocol specification; urgent radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
	ccurring after a surgical procedur		Figure 4 and 5 70 f	I the share to the	D		
Postoperative thoracic procedure complication	-	Extubated within 24 - 72 hrs postoperatively	Extubated >72 hrs postoperatively, but before tracheostomy indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death		
Definition: A finding of a previous	ly undocumented problem that oc	curs after a thoracic procedure.	1	I			
Prolapse of intestinal stoma	Asymptomatic; reducible	Recurrent after manual reduction; local irritation or stool leakage; difficulty to fit appliance; limiting instrumental	Severe symptoms; elective operative intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death		

Injury, poisoning and procedural complications							
			Grade		I		
Adverse Event	1	2	3	4	5		
	of the intestinal stoma (surgically				l		
Prolapse of urostomy	Asymptomatic; clinical or	Local care or maintenance;	Dysfunctional stoma; elective	Life-threatening consequences;	Death		
	diagnostic observations only;	minor revision indicated	operative intervention or major	urgent intervention indicated			
	intervention not indicated		stomal revision indicated		l		
Definition: A finding of displacem	ent of the urostomy.		T	<u> </u>			
Radiation recall reaction	Faint erythema or dry	Moderate to brisk erythema;	Moist desquamation in areas	Life-threatening consequences;	Death		
(dermatologic)	desquamation	patchy moist desquamation,	other than skin folds and	skin necrosis or ulceration of full			
		mostly confined to skin folds	creases; bleeding induced by	thickness dermis; spontaneous			
		and creases; moderate edema	minor trauma or abrasion	bleeding from involved site; skin graft indicated			
Definition: A finding of courts okin	inflammatany reaction soused by	druge conscielly shamethereneys	 	1-	l .to=room		
-	inflammatory reaction caused by liting inflammatory reaction caused by liting inflammatory inflammatory inflammatory inflammatory.		-	lowing radiotrierapy. The initamina	itory reac		
Rectal anastomotic leak	Asymptomatic diagnostic	Symptomatic; medical		Life threatening concequences:	Death		
Aectal allastolliotic leak	observations only; intervention	intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative	Life-threatening consequences; urgent operative intervention	Death		
	not indicated	intervention indicated	intervention indicated	indicated			
Definition: A finding of leakage d	ue to breakdown of a rectal anasto	I Imposis (surgical connection of two	'	I	ı		
Seroma	Asymptomatic; clinical or	Symptomatic; simple aspiration	Symptomatic, elective radiologic	-	-		
	diagnostic observations only; intervention not indicated	indicated	or operative intervention indicated				
Definition A finding of towns 19	1	I	maloatou	I	l		
	collection of serum in the tissues.			I			
Small intestinal anastomotic	Asymptomatic diagnostic	Symptomatic; medical	Severe symptoms; radiologic,	Life-threatening consequences;	Death		
leak	observations only; intervention	intervention indicated	endoscopic or elective operative intervention indicated				
	not indicated	l	ı	indicated	l		
	ue to breakdown of an anastomosi		arate anatomic structures) in the si				
Spermatic cord anastomotic	Asymptomatic diagnostic	Symptomatic; medical	Severe symptoms; radiologic,	Life-threatening consequences;	Death		
leak	observations only; intervention	intervention indicated	endoscopic or elective operative	urgent operative intervention			
	not indicated		intervention indicated	indicated			
Definition: A finding of leakage de	ue to breakdown of a spermatic co	ord anastomosis (surgical connecti	on of two separate anatomic struc	tures).			
Spinal fracture	Mild back pain; nonprescription	Moderate back pain;	Severe back pain;	Life-threatening consequences;	Death		
	analgesics indicated	prescription analgesics	hospitalization or intervention	symptoms associated with			
		indicated; limiting instrumental	indicated for pain control (e.g.,	neurovascular compromise			
		ADL	vertebroplasty); limiting self care ADL; disability				
D-6-iti		 	, ,	ļ	l		
	injury to the spine in which the con				ı		
Stenosis of gastrointestinal	-	Symptomatic; IV fluids indicated	Severely altered GI function;	Life-threatening consequences;	Death		
stoma		<24 hrs; manual dilation at bedside	tube feeding, TPN or hospitalization indicated;	urgent operative intervention indicated			
		bedside	elective operative intervention	indicated			
			indicated				
Definition: A finding of parrowing	of the gastrointestinal stoma (surg	। pically created opening on the surf	I	!	ı		
Stomal ulcer	Asymptomatic; clinical or	Symptomatic; medical	Severe symptoms; elective		_		
Storial dicer	diagnostic observations only;	intervention indicated	operative intervention indicated	-	-		
	intervention not indicated	intervention indicated	operative intervention indicated				
Definition: Δ disorder characteriz	। ed by a circumscribed, inflammato	I ary and necrotic erosive lesion on t	l ha jajunal mucosal surfaca closa t	I to the anastomosis site following a			
gastroenterostomy procedure.	52 5, a onoamoonboa, milaminato	., 110010110 0100110 1001011 011 1	jojaniai maooodi sundoo olose l	.s and anadomodis site following a			
Tracheal hemorrhage	Minimal bleeding identified on	Moderate bleeding; medical	Severe bleeding; transfusion	Life-threatening consequences;	Death		
	clinical or diagnostic exam;	intervention indicated	indicated; radiologic or	urgent intervention indicated			
	intervention not indicated		endoscopic intervention				
			indicated				
Definition: A finding of bleeding for	rom the trachea.						
Fracheal obstruction	Partial asymptomatic	Symptomatic (e.g., noisy airway	Stridor; radiologic or endoscopic	Life-threatening airway	Death		
	obstruction on examination	breathing), no respiratory	intervention indicated (e.g.,	compromise; urgent intervention	Joann		
	(e.g., visual, radiologic or	distress; medical intervention	stent, laser); limiting self care	indicated (e.g., tracheotomy or			
	endoscopic)	indicated (e.g., steroids); limiting		intubation)			
	. ,	instrumental ADL		,			
	1	1	!	•	•		

Grade							
Adverse Event	1	2	3	4	5		
Tracheostomy site bleeding	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A finding of blood lea	kage from the tracheostomy site.	+					
Ureteric anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
	due to breakdown of a ureteral ana	T i		T .			
Jrethral anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A finding of leakage of	due to breakdown of a urethral ana	stomosis (surgical connection of t	vo separate anatomic structures).				
Urostomy leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A finding of leakage of	of contents from a urostomy.	1	1	T			
Urostomy obstruction	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; dilation or endoscopic repair or stent placement indicated	Altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); elective operative intervention indicated	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death		
Definition: A finding of blockage	of the urostomy.						
Urostomy site bleeding	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A finding of bleeding	from the urostomy site.	'	'	'	•		
Urostomy stenosis	-	Symptomatic but no hydronephrosis, no sepsis or no renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic (e.g., hydronephrosis, or renal dysfunction); elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A finding of narrowinຸ	g of the opening of a urostomy.						
Uterine anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A finding of leakage of	due to breakdown of a uterine anas	tomosis (surgical connection of tw	o separate anatomic structures).				
Uterine perforation	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
	zed by a rupture in the uterine wall.		0		D41-		
/aginal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A finding of leakage of	due to breakdown of a vaginal anas	stomosis (surgical connection of tw	o separate anatomic structures).		1		
/as deferens anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A finding of leakage of	due to breakdown of a vas deferens	s anastomosis (surgical connection	n of two separate anatomic structu	res).			
Vascular access complication	-	Device dislodgement, blockage, leak, or malposition; device replacement indicated	Deep vein or cardiac thrombosis; intervention indicated (e.g., anticoagulation, lysis, filter, invasive procedure)	Embolic event including pulmonary embolism or life-threatening thrombus	Death		

	Injury	, poisoning and procedu	ral complications		
			Grade		
Adverse Event	1	2	3	4	5
Venous injury	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); repair or revision not indicated	Severe symptoms; limiting self care ADL; repair or revision indicated; disabling	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to	a vein.				
Wound complication	Incisional separation of <=25% of wound, no deeper than superficial fascia	Incisional separation >25% of wound; local care indicated	Hernia without evidence of strangulation; fascial disruption/dehiscence; primary wound closure or revision by operative intervention indicated	Hernia with evidence of strangulation; major reconstruction flap, grafting, resection, or amputation indicated	Death
Wound dehiscence	Incisional separation of <=25%	Incisional separation >25% of	Fascial disruption or dehiscence	Life-threatening consequences;	Death
wound deniscence	of wound, no deeper than superficial fascia	wound with local care; asymptomatic hernia or symptomatic hernia without evidence of strangulation	without evisceration; primary wound closure or revision by operative intervention indicated	Lire-inreatening consequences; symptomatic hernia with evidence of strangulation; fascial disruption with evisceration; major reconstruction flap, grafting, resection, or amputation indicated	Death
Definition: A finding of separation	of the approximated margins of a	surgical wound.	T	T	
Wrist fracture	Mild; non-surgical intervention indicated	Limiting instrumental ADL; operative intervention indicated	Limiting self care ADL; elective surgery indicated	-	-
Definition: A finding of traumatic	injury to the wrist joint in which the	continuity of a wrist bone is broke	en.		
Injury, poisoning and procedural complications - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

		Investigations	S		
			Grade		
Adverse Event	1	2	3	4	5
Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage	-	-
	y test result in which the partial th			possible indicator of coagulopat	hy, a prolonge
	may occur in a variety of disease				
Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
	oratory test results that indicate a		1 ,	1	T
Alkaline phosphatase increased	1	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
	oratory test results that indicate a		1		
Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on lab	oratory test results that indicate a	n increase in the level of aspartate	aminotransferase (AST or SGOT) in a blood specimen.	_
Blood antidiuretic hormone abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Hospitalization indicated	-	-
Definition: A finding based on lab	oratory test results that indicate a	bnormal levels of antidiuretic horm	one in the blood specimen.		
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN	-
Definition: A finding based on lab	oratory test results that indicate a	n abnormally high level of bilirubin	in the blood. Excess bilirubin is as	ssociated with jaundice.	
Blood corticotrophin decreased	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Hospitalization indicated	-	-
Definition: A finding based on lab	oratory test results that indicate a	n decrease in levels of corticotropl	nin in a blood specimen.		
Blood gonadotrophin abnormal	Asymptomatic; clinical or diagnostic observations only;	Symptomatic; medical intervention indicated; limiting	Severe symptoms; limiting self care ADL	-	-
Definition A finding board on lab	intervention not indicated	instrumental ADL			l
	oratory test results that indicate a	1	ormone in a blood specimen.		1
Blood prolactin abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	-	-	-
Definition: A finding based on lab	oratory test results that indicate a	, bnormal levels of prolactin hormor	ne in a blood specimen.	'	•
Carbon monoxide diffusing capacity decreased	3 - 5 units below LLN; for follow- up, a decrease of 3 - 5 units (ml/min/mm Hg) below the baseline value	6 - 8 units below LLN; for follow- up, an asymptomatic decrease of >5 - 8 units (ml/min/mm Hg) below the baseline value	Asymptomatic decrease of >8 units drop; >5 units drop along with the presence of pulmonary symptoms (e.g., >Grade 2 hypoxia or >Grade 2 or higher dyspnea)	-	-
Definition: A finding based on lun	g function test results that indicate	a decrease in the lung capacity	to absorb carbon monoxide.	'	•
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer	-	-
· · · · · · · · · · · · · · · · · · ·	t which indicates increased levels	of cardiac troponin I in a biologica T	1		
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer	-	-
Definition: A laboratory test resul	t which indicates increased levels	of cardiac troponin T in a biologica	al specimen.		
CD4 lymphocytes decreased	<lln -="" 0.5="" 500="" <lln="" mm3;="" x<br="">10e9 /L</lln>	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200 - 50/mm3; <0.2 x 0.05 - 10e9 /L	<50/mm3; <0.05 x 10e9 /L	-
Definition: A finding based on lab	oratory test results that indicate a	n decrease in levels of CD4 lymph	ocytes in a blood specimen.		
Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L	-
Definition: A finding based on lab	oratory test results that indicate h	igher than normal levels of cholest	terol in a blood specimen.		
CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN	-
Definition: A finding based on lab	oratory test results that indicate a	n increase in levels of creatine pho	osphokinase in a blood specimen.	· 	<u> </u>

		Investigations	<u> </u>		
			Grade		
Adverse Event	1	2	3	4	5
Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	-
Definition: A finding based on lab	oratory test results that indicate in	creased levels of creatinine in a b	iological specimen.	I	
Ejection fraction decreased	-	Resting ejection fraction (EF) 50 - 40%; 10 - 19% drop from baseline	Resting ejection fraction (EF) 39 - 20%; >20% drop from baseline	Resting ejection fraction (EF) <20%	-
Definition: The percentage compo	uted when the amount of blood eje	ected during a ventricular contracti	on of the heart is compared to the	amount that was present prior to	the
Electrocardiogram QT corrected interval prolonged		QTc 481 - 500 ms	QTc >= 501 ms on at least two separate ECGs	QTc >= 501 or >60 ms change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	-
· ·	i i	bnormally long corrected QT inter			1
Fibrinogen decreased	<1.0 - 0.75 x LLN or <25% decrease from baseline	<0.75 - 0.5 x LLN or 25 - <50% decrease from baseline	<0.5 - 0.25 x LLN or 50 - <75% decrease from baseline	<0.25 x LLN or 75% decrease from baseline or absolute value <50 mg/dL	-
Definition: A finding based on lab	oratory test results that indicate a	n decrease in levels of fibrinogen i	n a blood specimen.	'	•
Forced expiratory volume decreased	FEV1% (percentages of observed FEV1 and FVC related to their respective predicted values) 99 - 70% predicted	FEV1 60 - 69%	50 - 59%	<= 49%	-
Definition: A finding based on tes	t results that indicate a relative de	crease in the fraction of the forced	vital capacity that is exhaled in a	specific number of seconds.	
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
		igher than normal levels of the enz			nma-
		roup from a gamma glutamyl pept	ide to another peptide, amino acid	s or water.	
Growth hormone abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	-	-	-
Definition: A finding based on lab	oratory test results that indicate a	bnormal levels of growth hormone	in a biological specimen.		
Haptoglobin decreased	<lln< td=""><td>-</td><td>-</td><td>-</td><td>-</td></lln<>	-	-	-	-
Definition: A finding based on lab	oratory test results that indicate a	n decrease in levels of haptoglobir	n in a blood specimen.		
Hemoglobin increased	Increase in >0 - 2 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN	-	-
Definition: A finding based on lab	oratory test results that indicate in	creased levels of hemoglobin in a	biological specimen.		
INR increased	>1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation	-	-
Definition: A finding based on lab	oratory test results that indicate a	n increase in the ratio of the patier	t's prothrombin time to a control s	ample in the blood.	
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN	-
Definition: A finding based on lab	oratory test results that indicate a	n increase in the level of lipase in a	a biological specimen.		
Lymphocyte count decreased	<lln -="" 0.8="" 800="" <lln="" mm3;="" x<br="">10e9 /L</lln>	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	-
Definition: A finding based on lab	oratory test results that indicate a	decrease in number of lymphocyte	es in a blood specimen.		
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	-
Definition: A finding based on lab	oratory test results that indicate a	n abnormal increase in the numbe	r of lymphocytes in the blood, effu	sions or bone marrow.	
Neutrophil count decreased	<lln -="" 1.5="" 1500="" <lln="" mm3;="" x<br="">10e9 /L</lln>	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-
Definition: A finding based on lab	oratory test results that indicate a	decrease in number of neutrophils	s in a blood specimen.		
Pancreatic enzymes decreased	<lln and="" asymptomatic<="" td=""><td>Increase in stool frequency, bulk, or odor; steatorrhea</td><td>Sequelae of absorption deficiency</td><td>-</td><td>-</td></lln>	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency	-	-
Definition: A finding boood on lab	oratory test results that indicate a	n decrease in levels of pancreatic	enzymes in a biological specimen.		

		Investigations			
			Grade		
Adverse Event	1	2	3	4	5
Platelet count decreased	<lln -="" -<="" 75,000="" <lln="" mm3;="" td=""><td><75,000 - 50,000/mm3; <75.0 -</td><td><50,000 - 25,000/mm3; <50.0 -</td><td><25,000/mm3; <25.0 x 10e9 /L</td><td>-</td></lln>	<75,000 - 50,000/mm3; <75.0 -	<50,000 - 25,000/mm3; <50.0 -	<25,000/mm3; <25.0 x 10e9 /L	-
	75.0 x 10e9 /L	50.0 x 10e9 /L	25.0 x 10e9 /L		
Definition: A finding based on lab	poratory test results that indicate a	decrease in number of platelets in	a blood specimen.		
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN	-
Definition: A finding based on lab	oratory test results that indicate a	n increase in the levels of amylase	in a serum specimen.		
Urine output decreased	-	-	Oliguria (<80 ml in 8 hr)	Anuria (<240 ml in 24 hr)	-
Definition: A finding based on tes	st results that indicate urine produc	ction is less relative to previous ou	tput.	•	
Vital capacity abnormal	90 - 75% of predicted value	<75 - 50% of predicted value;	<50% of predicted value;	-	-
		limiting instrumental ADL	limiting self care ADL		
Definition: A finding based on pu value.	Imonary function test results that in	ndicate an abnormal vital capacity	(amount of exhaled after a maxim	um inhalation) when compared to	the predicted
Weight gain	5 - <10% from baseline	10 - <20% from baseline	>=20% from baseline	-	-
Definition: A finding characterize	d by an increase in overall body w	eight; for pediatrics, greater than t	he baseline growth curve.		
Weight loss	5 to <10% from baseline;	10 - <20% from baseline;	>=20% from baseline; tube	-	-
	intervention not indicated	nutritional support indicated	feeding or TPN indicated		
Definition: A finding characterize	d by a decrease in overall body we	eight; for pediatrics, less than the b	paseline growth curve.		
White blood cell decreased	<lln -="" 3.0="" 3000="" <lln="" mm3;="" td="" x<=""><td><3000 - 2000/mm3; <3.0 - 2.0 x</td><td><2000 - 1000/mm3; <2.0 - 1.0 x</td><td><1000/mm3; <1.0 x 10e9 /L</td><td>-</td></lln>	<3000 - 2000/mm3; <3.0 - 2.0 x	<2000 - 1000/mm3; <2.0 - 1.0 x	<1000/mm3; <1.0 x 10e9 /L	-
	10e9 /L	10e9 /L	10e9 /L		
Definition: A finding based on lab	poratory test results that indicate a	n decrease in number of white blo	od cells in a blood specimen.		
Investigations - Other, specify	Asymptomatic or mild	Moderate; minimal, local or	Severe or medically significant	Life-threatening consequences;	Death
	symptoms; clinical or diagnostic	noninvasive intervention	but not immediately life-	urgent intervention indicated	
	observations only; intervention	indicated; limiting age-	threatening; hospitalization or		
	not indicated	appropriate instrumental ADL	prolongation of existing		
			hospitalization indicated;		
			disabling; limiting self care ADL		

		Metabolism and nutrition	n disorders					
Grade								
Adverse Event	1	2	3	4	5			
cidosis	pH <normal, but="">=7.3</normal,>	-	pH <7.3	Life-threatening consequences	Death			
efinition: A disorder characteriz	zed by abnormally high acidity (high	h hydrogen-ion concentration) of t	he blood and other body tissues.	1				
Alcohol intolerance	-	Present	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characterized in the comiting, indigestion and headage in the comiting in the community of the communi	zed by an increase in sensitivity to	the adverse effects of alcohol, wh	ich can include nasal congestion,	skin flushes, heart dysrhythmias,	nausea,			
Alkalosis	pH >normal, but <=7.5		pH >7.5	Life-threatening consequences	Death			
	1.	-	1.	Life-tiffeaterining consequences	Death			
	zed by abnormally high alkalinity (lo			1 :5- 41	D41-			
Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteriz	zed by a loss of appetite.							
Dehydration	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated <24 hrs	IV fluids or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteriz	zed by excessive loss of water from	n the body. It is usually caused by	severe diarrhea, vomiting or diaph	noresis.				
Glucose intolerance	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; dietary modification or oral agent indicated	Severe symptoms; insulin indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteriz	zed by an inability to properly metal	bolize glucose.	1					
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; lonized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; lonized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; lonized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; lonized calcium >1.8 mmol/L; life-threatening consequences	Death			
Definition: A disorder characteriz	zed by laboratory test results that ir	ndicate an elevation in the concen	tration of calcium (corrected for all	bumin) in blood.				
Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences	Death			
Definition: A disorder characteriz	zed by laboratory test results that in	ndicate an elevation in the concen	tration of blood sugar. It is usually	an indication of diabetes mellitus	or glucose			
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences	Death			
Definition: A disorder characterize the use of diuretic drugs.	zed by laboratory test results that ir	ndicate an elevation in the concen	tration of potassium in the blood; a	associated with kidney failure or so	ometimes w			
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences	Death			
Definition: A disorder characterization	zed by laboratory test results that ir	ndicate an elevation in the concen	tration of magnesium in the blood		1			
lypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death			
Definition: A disorder characterization	zed by laboratory test results that ir	ndicate an elevation in the concen	tration of sodium in the blood.	T	1			
lypertriglyceridemia	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L; life-threatening consequences	Death			
efinition: A disorder characterization	zed by laboratory test results that ir	ndicate an elevation in the concen	tration of triglyceride concentration	n in the blood.				
lyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences	>10 mg/dL; >0.59 mmol/L; life- threatening consequences	Death			
efinition: A disorder characteriz	zed by laboratory test results that ir	ndicate an elevation in the concen	tration of uric acid.					
lypoalbuminemia	<lln -="" 3="" 30="" <lln="" dl;="" g="" l<="" td=""><td><3 - 2 g/dL; <30 - 20 g/L</td><td><2 g/dL; <20 g/L</td><td>Life-threatening consequences; urgent intervention indicated</td><td>Death</td></lln>	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated	Death			
efinition: A disorder characteriz	zed by laboratory test results that ir	ndicate a low concentration of albu	umin in the blood.					

		Metabolism and nutrition	n disorders		
			Grade		
Adverse Event	1	2	3	4	5
Hypocalcemia	Corrected serum calcium of <lln -="" 2.0<br="" 8.0="" <lln="" dl;="" mg="">mmol/L; lonized calcium <lln -<br="">1.0 mmol/L</lln></lln>	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; lonized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; lonized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; Iife-threatening consequences	Death
Definition: A disorder characterize	ed by laboratory test results that ir	ndicate a low concentration of calc	ium (corrected for albumin) in the	blood.	,
Hypoglycemia	<lln -="" 3.0="" 55="" <lln="" dl;="" l<="" mg="" mmol="" td=""><td><55 - 40 mg/dL; <3.0 - 2.2 mmol/L</td><td><40 - 30 mg/dL; <2.2 - 1.7 mmol/L</td><td><30 mg/dL; <1.7 mmol/L; life- threatening consequences; seizures</td><td>Death</td></lln>	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life- threatening consequences; seizures	Death
Definition: A disorder characteriz	ed by laboratory test results that ir	ndicate a low concentration of gluc	ose in the blood.		
Hypokalemia	<lln -="" 3.0="" l<="" mmol="" td=""><td><lln -="" 3.0="" l;<br="" mmol="">symptomatic; intervention indicated</lln></td><td><3.0 - 2.5 mmol/L; hospitalization indicated</td><td><2.5 mmol/L; life-threatening consequences</td><td>Death</td></lln>	<lln -="" 3.0="" l;<br="" mmol="">symptomatic; intervention indicated</lln>	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death
Definition: A disorder characteriz	ed by laboratory test results that ir	ndicate a low concentration of pota	assium in the blood.		
Hypomagnesemia	<lln -="" 0.5="" 1.2="" <lln="" dl;="" l<="" mg="" mmol="" td=""><td><1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L</td><td><0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L</td><td><0.7 mg/dL; <0.3 mmol/L; life-threatening consequences</td><td>Death</td></lln>	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; life-threatening consequences	Death
Definition: A disorder characteriz	ed by laboratory test results that in	ndicate a low concentration of mag	nesium in the blood.		
Hyponatremia	<lln -="" 130="" l<="" mmol="" td=""><td>-</td><td><130 - 120 mmol/L</td><td><120 mmol/L; life-threatening consequences</td><td>Death</td></lln>	-	<130 - 120 mmol/L	<120 mmol/L; life-threatening consequences	Death
Definition: A disorder characteriz	ed by laboratory test results that ir	ndicate a low concentration of sod	um in the blood.		
Hypophosphatemia	<lln -="" 0.8="" 2.5="" <lln="" dl;="" l<="" mg="" mmol="" td=""><td><2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L</td><td><2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L</td><td><1.0 mg/dL; <0.3 mmol/L; life- threatening consequences</td><td>Death</td></lln>	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L	<1.0 mg/dL; <0.3 mmol/L; life- threatening consequences	Death
Definition: A disorder characteriz	ed by laboratory test results that in	ndicate a low concentration of pho	sphates in the blood.		
Iron overload	-	Moderate symptoms; intervention not indicated	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by accumulation of iron in the ti	issues.			
Obesity	-	BMI 25 - 29.9 kg/m2	BMI 30 - 39.9 kg/m2	BMI >=40 kg/m2	-
Definition: A disorder characteriz	ed by having a high amount of boo	dy fat.			
Tumor lysis syndrome	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by metabolic abnormalities that	t result from a spontaneous or the	rapy-related cytolysis of tumor cell	S	
Metabolism and nutrition disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

	Muscu	loskeletal and connectiv	e tissue disorders					
	Grade							
Adverse Event	1	2	3	4	5			
Abdominal soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g. tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteriz	ed by a necrotic process occurring	g in the soft tissues of the abdomir	nal wall.					
Arthralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characteriz	red by a sensation of marked disco	omfort in a joint.	1	T				
Arthritis	Mild pain with inflammation, erythema, or joint swelling	Moderate pain associated with signs of inflammation, erythema, or joint swelling; limiting instrumental ADL	Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self care ADL	-	-			
Definition: A disorder characteriz	ed by inflammation involving a join	nt.	1	1				
Avascular necrosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
	ed by necrotic changes in the boned the destruction of the bone struction.		od supply. Most often affecting the	epiphysis of the long bones, the n	ecrotic			
Back pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characteriz	ed by marked discomfort sensation	n in the back region.						
Bone pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characteriz	ed by marked discomfort sensatio	n in the bones.	1	I				
Buttock pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characteriz	ed by marked discomfort sensation	n in the buttocks.						
Chest wall pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characteriz	ed by marked discomfort sensation	n in the chest wall region.						
Exostosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	-	-			
Definition: A disorder characteriz	ed by non-neoplastic overgrowth	of bone.						
Fibrosis deep connective tissue	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration; unable to slide or pinch skin; limiting joint or orifice movement (e.g. mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death			
Definition: A disorder characteriz	ted by fibrotic degeneration of the	deep connective tissues.	T	T				
Flank pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characteriz	ed by marked discomfort sensation	n on the lateral side of the body in	the region below the ribs and abo	ove the hip.				
Generalized muscle weakness	Symptomatic; weakness perceived by patient but not evident on physical exam	Symptomatic; weakness evident on physical exam; weakness limiting instrumental ADL	ADL; disabling	-	-			
Definition: A disorder characteriz	red by a reduction in the strength o	of muscles in multiple anatomic sit	es.	T				
Growth suppression	Reduction in growth velocity by 10 - 29% ideally measured over the period of a year ted by of stature that is smaller that	Reduction in growth velocity by 30 - 49% ideally measured over the period of a year or 0 - 49% reduction in growth from the baseline growth curve	Reduction in growth velocity of >=50% ideally measured over the period of a year	-	-			

Grade							
Adverse Event	1	2	3	4	5		
Head soft tissue necrosis	-	Local wound care; medical	Operative debridement or other	Life-threatening consequences;	Death		
		intervention indicated (e.g.,	invasive intervention indicated	urgent intervention indicated			
		dressings or topical	(e.g., tissue reconstruction, flap				
		medications)	or grafting)				
Definition: A disorder characterize	ed by a necrotic process occurring	in the soft tissues of the head.		!			
Joint effusion	Asymptomatic; clinical or	Symptomatic; limiting	Severe symptoms; limiting self	-	-		
	diagnostic observations only;	instrumental ADL	care ADL; elective operative				
	intervention not indicated	in or arrivation at 7 to 2	intervention indicated; disabling				
Definition: A disorder characterize	ed by excessive fluid in a joint, usu	। ually as a result of joint inflammati	- 1	l	ı		
Joint range of motion decreased		>25 - 50% decrease in ROM;	>50% decrease in ROM; limiting	_			
Joint range of motion decreased	motion); decreased ROM	limiting instrumental ADL	self care ADL; disabling	-	-		
	limiting athletic activity	Illiniung instrumental ADL	Sell Care ADE, disabiling				
Definition: A disorder characteriz		of any joint	I		l		
	ed by a decrease in joint flexibility						
Joint range of motion decreased	Mild restriction of rotation or	Rotation <60 degrees to right or	Ankylosed/fused over multiple	=	-		
cervical spine	flexion between 60 - 70 degrees	left; <60 degrees of flexion	segments with no C-spine				
			rotation		l		
	ed by a decrease in flexibility of a	. ,			1		
Joint range of motion decreased	Stiffness; difficulty bending to	Pain with range of motion	<50% lumbar spine flexion;	-	-		
lumbar spine	the floor to pick up a very light	(ROM) in lumbar spine; requires	associated with symptoms of				
	object but able to do athletic	a reaching aid to pick up a very	ankylosis or fused over multiple				
	activity	light object from the floor	segments with no L-spine				
			flexion (e.g., unable to reach to				
			floor to pick up a very light				
			object)				
Definition: A disorder characterize	ed by a decrease in flexibility of a l	lumbar spine joint.					
Kyphosis	Asymptomatic; clinical or	Moderate accentuation; limiting	Severe accentuation; operative	-	-		
•	diagnostic observations only;	instrumental ADL	intervention indicated; limiting				
	intervention not indicated		self care ADL				
Definition: A disorder characterize	ed by an abnormal increase in the	curvature of the thoracic portion of	of the spine.				
Lordosis	Asymptomatic; clinical or	Moderate accentuation; limiting	Severe accentuation; operative	-	-		
	diagnostic observations only;	instrumental ADL	intervention indicated; limiting				
	intervention not indicated		self care ADL				
Definition: A disorder characterize	ed by an abnormal increase in the	curvature of the lumbar portion of	'	I	1		
Muscle weakness left-sided	Symptomatic; perceived by	Symptomatic; evident on	Limiting self care ADL; disabling	_	I _		
Widolo Wodinioos lon sidod	patient but not evident on	physical exam; limiting	Eliming son oute 7.52, dioasing				
	physical exam	instrumental ADL					
	1	l	l a body		l		
Definition: A disorder characterie		i uie illuscies oli lile lell side of l'il	c bouy.				
Definition: A disorder characterize	Symptomatic; perceived by	Symptomatic; evident on	Limiting self care ADL; disabling	-	-		
	Symptomatic; perceived by patient but not evident on	Symptomatic; evident on physical exam; limiting		-	-		
Muscle weakness lower limb	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL		-	-		
Muscle weakness lower limb Definition: A disorder characteriz	Symptomatic; perceived by patient but not evident on physical exam ed by a reduction in the strength o	Symptomatic; evident on physical exam; limiting instrumental ADL f the lower limb muscles.	Limiting self care ADL; disabling	-	-		
Muscle weakness lower limb Definition: A disorder characteriz	Symptomatic; perceived by patient but not evident on physical exam ed by a reduction in the strength o Symptomatic; perceived by	Symptomatic; evident on physical exam; limiting instrumental ADL f the lower limb muscles. Symptomatic; evident on		-	-		
Muscle weakness lower limb	Symptomatic; perceived by patient but not evident on physical exam ed by a reduction in the strength o	Symptomatic; evident on physical exam; limiting instrumental ADL f the lower limb muscles. Symptomatic; evident on physical exam; limiting	Limiting self care ADL; disabling	-	-		
Muscle weakness lower limb Definition: A disorder characterize	Symptomatic; perceived by patient but not evident on physical exam ed by a reduction in the strength o Symptomatic; perceived by	Symptomatic; evident on physical exam; limiting instrumental ADL f the lower limb muscles. Symptomatic; evident on	Limiting self care ADL; disabling	-	-		
Muscle weakness lower limb Definition: A disorder characterize Muscle weakness right-sided	Symptomatic; perceived by patient but not evident on physical exam ed by a reduction in the strength o Symptomatic; perceived by patient but not evident on	Symptomatic; evident on physical exam; limiting instrumental ADL f the lower limb muscles. Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL; disabling Limiting self care ADL; disabling	-	-		
Muscle weakness lower limb Definition: A disorder characterize Muscle weakness right-sided	Symptomatic; perceived by patient but not evident on physical exam ed by a reduction in the strength o Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL f the lower limb muscles. Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL; disabling Limiting self care ADL; disabling		-		
Muscle weakness lower limb Definition: A disorder characteriz Muscle weakness right-sided Definition: A disorder characteriz	Symptomatic; perceived by patient but not evident on physical exam ed by a reduction in the strength o Symptomatic; perceived by patient but not evident on physical exam ed by a reduction in the strength o	Symptomatic; evident on physical exam; limiting instrumental ADL f the lower limb muscles. Symptomatic; evident on physical exam; limiting instrumental ADL f the muscles on the right side of	Limiting self care ADL; disabling Limiting self care ADL; disabling he body.		-		
Muscle weakness lower limb Definition: A disorder characteriz Muscle weakness right-sided Definition: A disorder characteriz	Symptomatic; perceived by patient but not evident on physical exam ed by a reduction in the strength o Symptomatic; perceived by patient but not evident on physical exam ed by a reduction in the strength o Symptomatic; perceived by	Symptomatic; evident on physical exam; limiting instrumental ADL f the lower limb muscles. Symptomatic; evident on physical exam; limiting instrumental ADL f the muscles on the right side of the Symptomatic; evident on	Limiting self care ADL; disabling Limiting self care ADL; disabling he body.		-		
Muscle weakness lower limb Definition: A disorder characterize Muscle weakness right-sided Definition: A disorder characterize Muscle weakness trunk	Symptomatic; perceived by patient but not evident on physical exam ed by a reduction in the strength of Symptomatic; perceived by patient but not evident on physical exam ed by a reduction in the strength of Symptomatic; perceived by patient but not evident on	Symptomatic; evident on physical exam; limiting instrumental ADL f the lower limb muscles. Symptomatic; evident on physical exam; limiting instrumental ADL f the muscles on the right side of Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL; disabling Limiting self care ADL; disabling he body.		-		
Muscle weakness lower limb Definition: A disorder characterize Muscle weakness right-sided Definition: A disorder characterize Muscle weakness trunk Definition: A disorder characterize	Symptomatic; perceived by patient but not evident on physical exam ed by a reduction in the strength of Symptomatic; perceived by patient but not evident on physical exam ed by a reduction in the strength of Symptomatic; perceived by patient but not evident on physical exam ed by a reduction in the strength of symptomatic; perceived by patient but not evident on physical exam ed by a reduction in the strength of	Symptomatic; evident on physical exam; limiting instrumental ADL f the lower limb muscles. Symptomatic; evident on physical exam; limiting instrumental ADL f the muscles on the right side of the Symptomatic; evident on physical exam; limiting instrumental ADL f the trunk muscles.	Limiting self care ADL; disabling Limiting self care ADL; disabling the body. Limiting self care ADL; disabling	-	-		
Muscle weakness lower limb Definition: A disorder characterize Muscle weakness right-sided Definition: A disorder characterize Muscle weakness trunk	Symptomatic; perceived by patient but not evident on physical exam ed by a reduction in the strength of Symptomatic; perceived by patient but not evident on physical exam ed by a reduction in the strength of Symptomatic; perceived by patient but not evident on physical exam ed by a reduction in the strength of Symptomatic; perceived by a reduction in the strength of Symptomatic; perceived by	Symptomatic; evident on physical exam; limiting instrumental ADL f the lower limb muscles. Symptomatic; evident on physical exam; limiting instrumental ADL f the muscles on the right side of the Symptomatic; evident on physical exam; limiting instrumental ADL f the trunk muscles. Symptomatic; evident on	Limiting self care ADL; disabling Limiting self care ADL; disabling he body.	-	-		
Muscle weakness lower limb Definition: A disorder characterize Muscle weakness right-sided Definition: A disorder characterize Muscle weakness trunk Definition: A disorder characterize	Symptomatic; perceived by patient but not evident on physical exam ed by a reduction in the strength of Symptomatic; perceived by patient but not evident on physical exam ed by a reduction in the strength of Symptomatic; perceived by patient but not evident on physical exam ed by a reduction in the strength of symptomatic; perceived by patient but not evident on physical exam ed by a reduction in the strength of	Symptomatic; evident on physical exam; limiting instrumental ADL f the lower limb muscles. Symptomatic; evident on physical exam; limiting instrumental ADL f the muscles on the right side of the Symptomatic; evident on physical exam; limiting instrumental ADL f the trunk muscles.	Limiting self care ADL; disabling Limiting self care ADL; disabling the body. Limiting self care ADL; disabling	-	-		

Musculoskeletal and connective tissue disorders							
		Ι .	Grade				
Adverse Event	1	2	3	4	5		
Musculoskeletal deformity	Cosmetically and functionally insignificant hypoplasia	Deformity, hypoplasia, or asymmetry able to be remediated by prosthesis (e.g., shoe insert) or covered by clothing	Significant deformity, hypoplasia, or asymmetry, unable to be remediated by prosthesis or covered by clothing; disabling	-	-		
Definition: A disorder characteri	ized by of a malformation of the mu	sculoskeletal system.					
Myalgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-		
Definition: A disorder characteri	ized by marked discomfort sensatio	n originating from a muscle or gro	up of muscles.				
Myositis	Mild pain	Moderate pain associated with weakness; pain limiting instrumental ADL	Pain associated with severe weakness; limiting self care ADL	-	-		
Definition: A disorder characteri	ized by inflammation involving the s	keletal muscles.					
Neck pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-		
Definition: A disorder characteri	ized by marked discomfort sensatio	n in the neck area.	T				
Neck soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteri	ized by a necrotic process occurring	g in the soft tissues of the neck.					
Osteonecrosis of jaw	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (e.g., topical agents); limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteri	ized by a necrotic process occurring	in the bone of the mandible.					
Osteoporosis	Radiologic evidence of osteoporosis or Bone Mineral Density (BMD) t-score -1 to -2.5 (osteopenia); no loss of height or intervention indicated	BMD t-score <-2.5; loss of height <2 cm; anti-osteoporotic therapy indicated; limiting instrumental ADL	Loss of height >=2 cm; hospitalization indicated; limiting self care ADL	-	-		
Definition: A disorder characteri composition), resulting in increa	ized by reduced bone mass, with a ased fracture incidence.	decrease in cortical thickness and	in the number and size of the trab	peculae of cancellous bone (but no	ormal chemi		
Pain in extremity	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-		
Definition: A disorder characteri	zed by marked discomfort sensatio	n in the upper or lower extremities	· i.				
Pelvic soft tissue necrosis	- ized by a necrotic process occurring	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death		
Scoliosis	<20 degrees; clinically		>45 degrees; scapular				
Scoliosis	undetectable	>20 - 45 degrees; visible by forward flexion; limiting instrumental ADL	prominence in forward flexion; operative intervention indicated; limiting self care ADL; disabling		-		
Definition: A disorder characteri	ized by a malformed, lateral curvatu	re of the spine.	1	<u> </u>			
Soft tissue necrosis lower limb	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteri	ized by a necrotic process occurring	g in the soft tissues of the lower ex	tremity.	1			
Soft tissue necrosis upper limb	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death		

	Muscu	loskeletal and connectiv	e tissue disorders				
	Grade						
Adverse Event	1	2	3	4	5		
Superficial soft tissue fibrosis	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration; unable to slide or pinch skin; limiting joint or orifice movement (e.g., mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death		
Definition: A disorder characterize	ed by fibrotic degeneration of the s	superficial soft tissues.					
Trismus	Decreased ROM (range of motion) without impaired eating	Decreased ROM requiring small bites, soft foods or purees	Decreased ROM with inability to adequately aliment or hydrate orally	-	-		
Definition: A disorder characterize	ed by lack of ability to open the mo	outh fully due to a decrease in the	range of motion of the muscles of	mastication.			
Unequal limb length	Mild length discrepancy <2 cm	Moderate length discrepancy 2 - 5 cm; shoe lift indicated; limiting instrumental ADL		-	-		
Definition: A disorder characterize	ed by of a discrepancy between th	e lengths of the lower or upper ex	tremities.				
Musculoskeletal and connective tissue disorder - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death		

	Neoplasms benig	n, malignant and unspec	cified (incl cysts and poly	yps)				
		Grade						
Adverse Event	1	2	3	4	5			
Leukemia secondary to oncology chemotherapy	-	-	-	Present	Death			
Definition: A disorder characterize	ed by leukemia arising as a result	of the mutagenic effect of chemot	herapy agents.					
Myelodysplastic syndrome	-	-	-	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characterize	ed by insufficiently healthy hemata	poietic cell production by the bone	e marrow.					
Treatment related secondary malignancy	-	-	Non life-threatening secondary malignancy	Acute life-threatening secondary malignancy; blast crisis in leukemia	Death			
Definition: A disorder characterize	ed by development of a malignand	by most probably as a result of trea	atment for a previously existing ma	alignancy.				
Tumor pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characterize	ed by marked discomfort from a ne	eoplasm that may be pressing on	a nerve, blocking blood vessels, ir	nflamed or fractured from metastas	sis.			
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death			

		Nervous system dis	orders		
			Grade		
Adverse Event	1	2	3	4	5
Abducens nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by involvement of the abducen	s nerve (sixth cranial nerve).		<u> </u>	1
Accessory nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by involvement of the accessor	y nerve (eleventh cranial nerve).			
Acoustic nerve disorder NOS	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by involvement of the acoustic	nerve (eighth cranial nerve).		T	
Akathisia	Mild restlessness or increased motor activity	Moderate restlessness or increased motor activity; limiting instrumental ADL	Severe restlessness or increased motor activity; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by an uncomfortable feeling of	inner restlessness and inability to	stay still; this is a side effect of so	me psychotropic drugs.	
Amnesia	Mild; transient memory loss	Moderate; short term memory loss; limiting instrumental ADL	Severe; long term memory loss; limiting self care ADL	-	-
	ed by systematic and extensive lo	ss of memory.	lv		
Aphonia	-	-	Voicelessness; unable to speak	1	-
	ed by the inability to speak. It may	1		i i	D41-
Arachnoiditis	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
	ed by inflammation of the arachno	i i	1		
Ataxia	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; mechanical assistance indicated	-	-
Definition: A disorder characteriz	ed by lack of coordination of musc	le movements resulting in the imp	airment or inability to perform volu	intary activities.	
Brachial plexopathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by regional paresthesia of the l	orachial plexus, marked discomfor	t and muscle weakness, and limite	ed movement in the arm or hand.	
Central nervous system necrosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; corticosteroids indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by a necrotic process occurring	in the brain and/or spinal cord.	1	<u> </u>	1
Cerebrospinal fluid leakage	Post-craniotomy: asymptomatic; Post-lumbar puncture: transient headache; postural care indicated	Post-craniotomy: moderate symptoms; medical intervention indicated; Post-lumbar puncture: persistent moderate symptoms; blood patch indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by loss of cerebrospinal fluid in	to the surrounding tissues.	T	T	
Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	-	-
Definition: A disorder characteriz	ed by a conspicuous change in co	gnitive function.	1	<u> </u>	
Concentration impairment	Mild inattention or decreased level of concentration	Moderate impairment in attention or decreased level of concentration; limiting instrumental ADL	Severe impairment in attention or decreased level of concentration; limiting self care ADL	-	-
Definition: A disorder characteriz	ted by a deterioration in the ability	concentration; limiting instrumental ADL	concentration; limiting self care		

Nervous system disorders							
			Grade _		Ι _		
Adverse Event	1	2	3	4	5		
Depressed level of consciousness	Decreased level of alertness	Sedation; slow response to stimuli; limiting instrumental ADL	Difficult to arouse	Life-threatening consequences	Death		
Definition: A disorder characteri	zed by a decrease in ability to perc	eive and respond.	_		1		
Dizziness	Mild unsteadiness or sensation of movement	Moderate unsteadiness or sensation of movement; limiting instrumental ADL	Severe unsteadiness or sensation of movement; limiting self care ADL	-	-		
Definition: A disorder characteri	zed by a disturbing sensation of lig	htheadedness, unsteadiness, gidd	liness, spinning or rocking.				
Dysarthria	Mild slurred speech	Moderate impairment of articulation or slurred speech	Severe impairment of articulation or slurred speech	-	-		
Definition: A disorder characterization	zed by slow and slurred speech res	sulting from an inability to coordina	ate the muscles used in speech.		1		
Dysesthesia	Mild sensory alteration	Moderate sensory alteration; limiting instrumental ADL	Severe sensory alteration; limiting self care ADL	-	-		
Definition: A disorder characteri	zed by distortion of sensory percep	tion, resulting in an abnormal and	unpleasant sensation.				
Dysgeusia	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	-	-	-		
Definition: A disorder characteriz	zed by abnormal sensual experien	ce with the taste of foodstuffs; it ca	n be related to a decrease in the	sense of smell.			
Dysphasia	Awareness of receptive or expressive characteristics; not impairing ability to communicate	Moderate receptive or expressive characteristics; impairing ability to communicate spontaneously	Severe receptive or expressive characteristics; impairing ability to read, write or communicate intelligibly	-	-		
Definition: A disorder characteriz	zed by impairment of verbal comm	unication skills, often resulting from	n brain damage.		1		
Edema cerebral	-	-	-	Life-threatening consequences; urgent intervention indicated	-		
Definition: A disorder characterize	zed by swelling due to an excessiv	e accumulation of fluid in the brain	l. T	T	1		
Encephalopathy	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characterize	zed by a pathologic process involvi	ng the brain.	1	T	1		
Extrapyramidal disorder	Mild involuntary movements	Moderate involuntary movements; limiting instrumental ADL	Severe involuntary movements or torticollis; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteri	zed by abnormal, repetitive, involu	ntary muscle movements, frenzied	speech and extreme restlessness	5.			
Facial muscle weakness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-		
Definition: A disorder characterize	zed by a reduction in the strength o	of the facial muscles.	T	T			
Facial nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-		
Definition: A disorder characteriz	zed by involvement of the facial ne	rve (seventh cranial nerve).					
Glossopharyngeal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteri:	zed by involvement of the glossoph	naryngeal nerve (ninth cranial nerv	e).	T			
Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-		
Definition: A disorder characteri:	zed by a sensation of marked disco	omfort in various parts of the head	, not confined to the area of distrib	ution of any nerve.			
Hydrocephalus	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; intervention not indicated	Severe symptoms or neurological deficit; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteri	zed by an abnormal increase of ce	rebrospinal fluid in the ventricles o	f the brain.	i			
Hypersomnia	Mild increased need for sleep	Moderate increased need for	Severe increased need for sleep	-	-		

Definition: A disorder characteriz	Asymptomatic; clinical or diagnostic observations only; intervention not indicated ed by involvement of the hypoglos Asymptomatic; clinical or diagnostic observations only;	2 Moderate symptoms; limiting instrumental ADL	Grade 3 Severe symptoms; limiting self care ADL	4	5
Hypoglossal nerve disorder Definition: A disorder characterize	Asymptomatic; clinical or diagnostic observations only; intervention not indicated ed by involvement of the hypoglos Asymptomatic; clinical or diagnostic observations only;	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self	4	5
	diagnostic observations only; intervention not indicated ed by involvement of the hypoglos Asymptomatic; clinical or diagnostic observations only;	instrumental ADL		-	1
	Asymptomatic; clinical or diagnostic observations only;	sal nerve (twelfth cranial nerve)			-
Intracranial hemorrhage	diagnostic observations only;	T	1	T	
	intervention not indicated	Moderate symptoms; medical intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by bleeding from the cranium.				
Ischemia cerebrovascular	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	-	-	-
Definition: A disorder characterize damage.	ed by a decrease or absence of bl	ood supply to the brain caused by	obstruction (thrombosis or embol	ism) of an artery resulting in neuro	logical
IVth nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterize	ed by involvement of the trochlear	nerve (fourth cranial nerve).	1		
Lethargy	Mild symptoms; reduced alertness and awareness	Moderate symptoms; limiting instrumental ADL	-	-	-
Definition: A disorder characterize	ed by a decrease in consciousnes	s characterized by mental and phy	ysical inertness.	_	
Leukoencephalopathy	Asymptomatic; small focal T2/FLAIR hyperintensities; involving periventricular white matter or <1/3 of susceptible areas of cerebrum +/- mild increase in subarachnoid space (SAS) and/or mild ventriculomegaly	Moderate symptoms; focal T2/FLAIR hyperintensities, involving periventricular white matter extending into centrum semiovale or involving 1/3 to 2/3 of susceptible areas of cerebrum +/- moderate increase in SAS and/or moderate ventriculomegaly	Severe symptoms; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving 2/3 or more of susceptible areas of cerebrum +/- moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Life-threatening consequences; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving most of susceptible areas of cerebrum +/- moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Death
Definition: A disorder characteriz	ed by diffuse reactive astrocytosis	with multiple areas of necrotic foo	i without inflammation.		
Memory impairment	Mild memory impairment	Moderate memory impairment; limiting instrumental ADL	Severe memory impairment; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by a deterioration in memory fu	nction.			
Meningismus	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by neck stiffness, headache, ar	nd photophobia resulting from irrita	ation of the cerebral meninges.		
Movements involuntary	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterize	ed by uncontrolled and purposeles	ss movements.			1
Myelitis	Asymptomatic; mild signs (e.g., Babinski's reflex or Lhermitte's sign)	Moderate weakness or sensory loss; limiting instrumental ADL	Severe weakness or sensory loss; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
	ed by inflammation involving the s	i i	T in the second	marked discomfort and incontiner	nce.
Neuralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
	ed by intense painful sensation ald			<u> </u>	
Nystagmus	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
	ed by involuntary movements of th	T .	Ī_		
Oculomotor nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by involvement of the oculomot	tor nerve (third cranial nerve).	1	T	
Olfactory nerve disorder	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-

		Nervous system dis	orders		
		·	Grade		
Adverse Event	1	2	3	4	5
Paresthesia	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterize are experienced in the absence of		ensory neurons resulting in abnorr	mal cutaneous sensations of tinglin	ng, numbness, pressure, cold, and	warmth that
Peripheral motor neuropathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; assistive device indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by inflammation or degeneration	on of the peripheral motor nerves.		T	
Peripheral sensory neuropathy	Asymptomatic; loss of deep tendon reflexes or paresthesia	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by inflammation or degeneratio	on of the peripheral sensory nerves	S.	<u> </u>	
Phantom pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterize	ed by marked discomfort related to	o a limb or an organ that is remove	ed from or is not physically part of	the body.	
Presyncope	-	Present (e.g., near fainting)	-	-	-
Definition: A disorder characterize	ed by an episode of lightheadedne	ess and dizziness which may prec	ede an episode of syncope.	T	
Pyramidal tract syndrome	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
	ed by dysfunction of the corticospi nd a decrease in fine motor coord		I cord. Symptoms include an incre	ease in the muscle tone in the lower	er extremities,
Radiculitis	Mild symptoms	Moderate symptoms; limiting instrumental ADL; medical intervention indicated	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize connecting nerve root.	ed by inflammation involving a ner	rve root. Patients experience mark	led discomfort radiating along a ne	rve path because of spinal pressu	re on the
Recurrent laryngeal nerve palsy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	Severe symptoms; medical intervention indicated (e.g., thyroplasty, vocal cord injection)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by paralysis of the recurrent lar	ryngeal nerve.			
Reversible posterior leukoencephalopathy syndrome	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; abnormal imaging studies; limiting instrumental ADL	Severe symptoms; very abnormal imaging studies; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
	-	=		indings of posterior leukoencephal s an acute or subacute reversible o	
Seizure	Brief partial seizure; no loss of consciousness	Brief generalized seizure	Multiple seizures despite medical intervention	Life-threatening; prolonged repetitive seizures	Death
Definition: A disorder characterize	ed by a sudden, involuntary skelet	tal muscular contractions of cerebi	ral or brain stem origin.		
Sinus pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterize	ed by marked discomfort in the fac	ce, between the eyes, or upper tee	eth originating from the sinuses.	,	
Somnolence	Mild but more than usual drowsiness or sleepiness	Moderate sedation; limiting instrumental ADL	Obtundation or stupor	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by characterized by excessive	sleepiness and drowsiness.			
Spasticity	Mild or slight increase in muscle tone	Moderate increase in muscle tone and increase in resistance through range of motion	Severe increase in muscle tone and increase in resistance through range of motion	Life-threatening; unable to move active or passive range of motion	Death
Definition: A disorder characterize disturbances.	ed by increased involuntary muscl			i It results in gait, movement, and s	peech
Stroke	Asymptomatic or mild neurologic deficit; radiographic findings only	Moderate neurologic deficit	Severe neurologic deficit	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by a sudden loss of sensory fu	nction due to an intracranial vascu	ılar event.		
Syncope	-	-	Fainting; orthostatic collapse	-	-
Definition: A disorder characterize	ed by spontaneous loss of conscio	ousness caused by insufficient blo	od supply to the brain.		

		Nervous system dis	orders		
			Grade		
Adverse Event	1	2	3	4	5
Transient ischemic attacks	Mild neurologic deficit with or without imaging confirmation	Moderate neurologic deficit with or without imaging confirmation	-	-	-
Definition: A disorder characteriz	ed by a brief attack (less than 24 h	nours) of cerebral dysfunction of va	ascular origin, with no persistent n	eurological deficit.	
Tremor	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by the uncontrolled shaking mo	vement of the whole body or indiv	ridual parts.		
Trigeminal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by involvement of the trigemina	l nerve (fifth cranial nerve).			
Vagus nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by involvement of the vagus ne	rve (tenth cranial nerve).	•		
Vasovagal reaction	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz increase in the stimulation of the	ed by a sudden drop of the blood progression vagus nerve.	oressure, bradycardia, and periph	eral vasodilation that may lead to	loss of consciousness. It results fr	om an
Nervous system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

riegiia	incy, puerperium and pe	rinatal conditions				
Grade						
1	2	3	4	5		
-	-	-	-	Fetal loss at any gestational age		
ed by death in utero; failure of the	product of conception to show evi	dence of respiration, heartbeat, or	definite movement of a voluntary	muscle after		
t possibility of resuscitation.						
-	<10% percentile of weight for gestational age	<5% percentile of weight for gestational age	<1% percentile of weight for gestational age	-		
ed by inhibition of fetal growth resu	ılting in the inability of the fetus to	achieve its potential weight.				
•	,	Delivery of a liveborn infant at 24 to 28 weeks gestation	Delivery of a liveborn infant at 24 weeks of gestation or less	-		
ed by delivery of a viable infant be	fore the normal end of gestation.	Typically, viability is achievable be	tween the twentieth and thirty-sev	enth week of		
-	-	Unintended pregnancy	-	-		
ed by an unexpected pregnancy at	the time of conception.	•	•	'		
symptoms; clinical or diagnostic	intervention indicated; limiting	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated;	Life-threatening consequences; urgent intervention indicated	Death		
	ed by death in utero; failure of the t possibility of resuscitation. ed by inhibition of fetal growth result belivery of a liveborn infant at >34 to 37 weeks gestation and by delivery of a viable infant belivery of a viable i	ed by death in utero; failure of the product of conception to show evit possibility of resuscitation. -	ted by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or to possibility of resuscitation. - <10% percentile of weight for gestational age <5% percentile of we	to by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary to possibility of resuscitation. - <10% percentile of weight for gestational age <5% percentile of weight for gestational age <1% percentile of weight for gestat		

		Psychiatric disor	ders		
			Grade		
Adverse Event	1	2	3	4	5
Agitation	Mild mood alteration	Moderate mood alteration	not indicated	Life-threatening consequences; urgent intervention indicated	Death
	erized by a state of restlessness asso		irritability and tension.		1
Anorgasmia	Inability to achieve orgasm not adversely affecting relationship	Inability to achieve orgasm adversely affecting relationship	-	-	-
	erized by an inability to achieve orgas				
Anxiety	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization not indicated	Life-threatening; hospitalization indicated	Death
Definition: A disorder characte stimulus.	erized by apprehension of danger and	d dread accompanied by restlessn	ess, tension, tachycardia, and dys	pnea unattached to a clearly iden	tifiable
Confusion	Mild disorientation	Moderate disorientation; limiting instrumental ADL	Severe disorientation; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	erized by a lack of clear and orderly the	nought and behavior.	1	1	Г
Delayed orgasm	Delay in achieving orgasm not adversely affecting relationship	Delay in achieving orgasm adversely affecting relationship	-	-	-
	erized by sexual dysfunction characte		1.		1
Delirium	Mild acute confusional state	Moderate and acute confusional state; limiting instrumental ADL	Severe and acute confusional state; limiting self care ADL; hospitalization indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characte reversible condition.	erized by the acute and sudden devel	opment of confusion, illusions, mo	ovement changes, inattentiveness,	agitation, and hallucinations. Usu	ally, it is a
Delusions		Moderate delucional eyentoms	Severe delucional symptoms:	Life threatening consequences	Death
Delusions	-	Moderate delusional symptoms	Severe delusional symptoms; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characte	erized by false personal beliefs held o	ontrary to reality, despite contradi	ctory evidence and common sens	e.	
Depression	Mild depressive symptoms	Moderate depressive symptoms; limiting instrumental ADL	Severe depressive symptoms; limiting self care ADL; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characte	erized by melancholic feelings of grief	or unhappiness.			
Euphoria	Mild mood elevation	Moderate mood elevation	Severe mood elevation (e.g., hypomania)	-	-
Definition: A disorder characte	erized by an exaggerated feeling of w	ell-being which is disproportionate	to events and stimuli.		
Hallucinations	Mild hallucinations (e.g., perceptual distortions)	Moderate hallucinations	Severe hallucinations; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characte	erized by a false sensory perception i	n the absence of an external stime	ulus.		
Insomnia	Mild difficulty falling asleep, staying asleep or waking up early	Moderate difficulty falling asleep, staying asleep or waking up early	Severe difficulty in falling asleep, staying asleep or waking up early	-	-
Definition: A disorder characte	erized by difficulty in falling asleep an	d/or remaining asleep.			
Libido decreased	Decrease in sexual interest not adversely affecting relationship	Decrease in sexual interest adversely affecting relationship	-	-	-
Definition: A disorder characte	erized by a decrease in sexual desire	T	1	1	Г
Libido increased	Mild increase in sexual interest not adversely affecting relationship	Moderate increase in sexual interest adversely affecting relationship	Severe increase in sexual interest leading to dangerous behavior	-	-
Definition: A disorder characte	erized by an increase in sexual desire	· ·	•	•	•
Mania	Mild manic symptoms (e.g., elevated mood, rapid thoughts, rapid speech, decreased need for sleep)	Moderate manic symptoms (e.g., relationship and work difficulties; poor hygiene)	Severe manic symptoms (e.g., hypomania; major sexual or financial indiscretions); hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characte	erized by excitement of psychotic prop	portions manifested by mental and	d physical hyperactivity, disorganiz	ation of behavior and elevation of	mood.
Personality change	Mild personality change	Moderate personality change	Severe personality change; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death

		Psychiatric disord	ders					
	Grade							
Adverse Event	1	2	3	4	5			
Definition: A disorder characterize	ed by a conspicuous change in a p	person's behavior and thinking.						
Psychosis	Mild psychotic symptoms	Moderate psychotic symptoms (e.g., disorganized speech; impaired reality testing)	Severe psychotic symptoms (e.g., paranoid; extreme disorganization); hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death			
Definition: A disorder characterize tumor.	ed by personality change, impaired	d functioning, and loss of touch wi	th reality. It may be a manifestatio	n of schizophrenia, bipolar disorde	er or brain			
Restlessness	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-			
Definition: A disorder characterize	ed by an inability to rest, relax or b	e still.						
Suicidal ideation	Increased thoughts of death but no wish to kill oneself	Suicidal ideation with no specific plan or intent	Specific plan to commit suicide without serious intent to die which may not require hospitalization	Specific plan to commit suicide with serious intent to die which requires hospitalization	-			
Definition: A disorder characterize	ed by thoughts of taking one's owr	n life.						
Suicide attempt	-	-	Suicide attempt or gesture without intent to die which may not require hospitalization	Suicide attempt with intent to die which requires hospitalization	Death			
Definition: A disorder characterize	ed by self-inflicted harm in an atter	mpt to end one's own life.						
Psychiatric disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; disabling; limiting self care ADL	Life-threatening consequences; hospitalization or urgent intervention indicated	Death			

Renal and urinary disorders								
Grade								
Adverse Event	1	2	3	4	5			
Acute kidney injury	Creatinine level increase of >0.3 mg/dL; creatinine 1.5 - 2.0 x above baseline	baseline	Creatinine >3 x baseline or >4.0 mg/dL; hospitalization indicated	Life-threatening consequences; dialysis indicated	Death			
Definition: A disorder characteri auses (ureteral or bladder outf	zed by the acute loss of renal funct low obstruction).	ion and is traditionally classified a	s pre-renal (low blood flow into kid	ney), renal (kidney damage) and բ	oost-renal			
Bladder perforation	-	Extraperitoneal perforation, indwelling catheter indicated	Intraperitoneal perforation; elective radiologic, endoscopic or operative intervention indicated	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death			
Definition: A disorder characteri	zed by a rupture in the bladder wall							
Bladder spasm	Intervention not indicated	Antispasmodics indicated	Hospitalization indicated	-	-			
Definition: A disorder characteri	zed by a sudden and involuntary co	ontraction of the bladder wall.		•				
Chronic kidney disease	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <lln -="" 60<br="">ml/min/1.73 m2 or proteinuria 2+ present; urine protein/creatinine >0.5</lln>	eGFR or CrCl 59 - 30 ml/min/1.73 m2	eGFR or CrCl 29 - 15 ml/min/1.73 m2	eGFR or CrCl <15 ml/min/1.73 m2; dialysis or renal transplant indicated	Death			
Definition: A disorder characteri	zed by gradual and usually perman	ent loss of kidney function resulting	ng in renal failure.					
Cystitis noninfective	Microscopic hematuria; minimal increase in frequency, urgency, dysuria, or nocturia; new onset of incontinence	Moderate hematuria; moderate increase in frequency, urgency, dysuria, nocturia or incontinence; urinary catheter placement or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death			
Definition: A disorder characteri	zed by inflammation of the bladder	which is not caused by an infection	on of the urinary tract.	•	•			
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated; limiting self care ADL	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death			
Definition: A disorder characteri	zed by laboratory test results that in	ndicate blood in the urine.		T	•			
Hemoglobinuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-			
Definition: A disorder characteri	zed by laboratory test results that ir	ndicate the presence of free hemo	oglobin in the urine.					
Proteinuria	1+ proteinuria; urinary protein <1.0 g/24 hrs	Adults: 2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Pediatric: urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Adults: urinary protein >=3.5 g/24 hrs; Pediatric: urine P/C >1.9	-	-			
Definition: A disorder characteri	zed by laboratory test results that ir	ndicate the presence of excessive	protein in the urine. It is predomin	antly albumin, but also globulin.				
Renal calculi	Asymptomatic or mild symptoms; occasional use of nonprescription analgesics indicated	Symptomatic; oral antiemetics indicated; around the clock nonprescription analgesics or any oral narcotic analgesics indicated	Hospitalization indicated; IV intervention (e.g., analgesics, antiemetics); elective endoscopic or radiologic intervention indicated	Life-threatening consequences; urgent radiologic, endoscopic or operative intervention indicated	Death			
Definition: A disorder characteri	zed by the formation of crystals in t	he pelvis of the kidney.	T	T				
Renal colic	Mild pain not interfering with activity; nonprescription medication indicated	Moderate pain; limiting instrumental ADL; prescription medication indicated	Hospitalization indicated; limiting self care ADL	-	-			

		Renal and urinary di	sorders		
			Grade		
Adverse Event	1	2	3	4	5
Renal hemorrhage	Mild symptoms; intervention not indicated	Analgesics and hematocrit monitoring indicated	Transfusion, radiation, or hospitalization indicated; elective radiologic, endoscopic or operative intervention indicated	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characteriz	ed by bleeding from the kidney.				
Urinary fistula	-	Noninvasive intervention indicated; urinary or suprapubic catheter placement indicated	Limiting self care ADL; elective radiologic, endoscopic or operative intervention indicated; permanent urinary diversion indicated	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characteriz	ed by an abnormal communication	between any part of the urinary s	system and another organ or anato	omic site.	
Urinary frequency	Present	Limiting instrumental ADL; medical management indicated	-	-	-
Definition: A disorder characteriz	ed by urination at short intervals.			T	1
Urinary incontinence	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous; pads indicated; limiting instrumental ADL	Intervention indicated (e.g., clamp, collagen injections); operative intervention indicated; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by inability to control the flow o	f urine from the bladder.			
Urinary retention	Urinary, suprapubic or intermittent catheter placement not indicated; able to void with some residual	Placement of urinary, suprapubic or intermittent catheter placement indicated; medication indicated	Elective operative or radiologic intervention indicated; substantial loss of affected kidney function or mass	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
Definition: A disorder characteriz	ed by accumulation of urine within	the bladder because of the inabil	ity to urinate.		
Urinary tract obstruction	Asymptomatic; clinical or diagnostic observations only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; urethral dilation, urinary or suprapubic catheter indicated	Symptomatic and altered organ function (e.g., hydronephrosis, or renal dysfunction); elective radiologic, endoscopic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by blockage of the normal flow	of contents of the urinary tract.			
Urinary tract pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by a sensation of marked disco	omfort in the urinary tract.			
Urinary urgency	Present	Limiting instrumental ADL; medical management indicated	-	-	-
Definition: A disorder characteriz	ed by a sudden compelling urge to	urinate.			
Urine discoloration	Present	-	-	-	-
Definition: A disorder characteriz	ed by a change in the color of the	urine.			•
Renal and urinary disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate, local or noninvasive intervention indicated; limiting instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

	Rep	productive system and b	reast disorders		
			Grade		
Adverse Event	1	2	3	4	5
Azoospermia	-	-	Absence of sperm in ejaculate	-	-
Definition: A disorder characte	erized by laboratory test results that ir	ndicate complete absence of speri	matozoa in the semen.		•
Breast atrophy	Minimal asymmetry; minimal	Moderate asymmetry; moderate	Asymmetry >1/3 of breast	-	-
	atrophy	atrophy	volume; severe atrophy		
Definition: A disorder characte	erized by underdevelopment of the br	east.	'	'	•
Breast pain	Mild pain	Moderate pain; limiting	Severe pain; limiting self care	-	_
,	·	instrumental ADL	ADL		
Definition: A disorder characte	erized by marked discomfort sensation	n in the breast region.	'	'	•
Dysmenorrhea	Mild symptoms; intervention not		Severe symptoms; limiting self	_	_
,	indicated	instrumental ADL	care ADL		
Definition: A disorder characte	rized by abnormally painful abdomin	al cramps during menses.	'	'	•
Dyspareunia	Mild discomfort or pain	Moderate discomfort or pain	Severe discomfort or pain	_	_
2)000.00	associated with vaginal	associated with vaginal	associated with vaginal		
	penetration; discomfort relieved	penetration; discomfort or pain	penetration; discomfort or pain		
	with use of vaginal lubricants or	partially relieved with use of	unrelieved by vaginal lubricants		
	estrogen	vaginal lubricants or estrogen	or estrogen		
Definition: A disorder characte	erized by painful or difficult coitus.		_		
Ejaculation disorder	Diminished ejaculation	Anejaculation or retrograde	-	-	-
		ejaculation			
Definition: A disorder characte	erized by problems related to ejaculat	ion. This category includes prema	ture, delayed, retrograde and pair	ıful ejaculation.	
Erectile dysfunction	Decrease in erectile function	Decrease in erectile function	Decrease in erectile function	-	-
	(frequency or rigidity of	(frequency/rigidity of erections),	(frequency/rigidity of erections)		
	erections) but intervention not	erectile intervention indicated,	but erectile intervention not		
	indicated (e.g., medication or	(e.g., medication or mechanical	helpful (e.g., medication or		
	use of mechanical device,	devices such as penile pump)	mechanical devices such as		
	penile pump)		penile pump); placement of a permanent penile prosthesis		
			indicated (not previously		
			present)		
Definition: A disorder characte	rized by the persistent or recurrent in	nability to achieve or to maintain a	n erection during sexual activity.	'	'
Fallopian tube obstruction	Diagnostic observations only;	Mild symptoms; elective	Severe symptoms; elective	_	_
anopian tago ogonaotion	intervention not indicated	intervention indicated	operative intervention indicated		
Definition: A disorder characte	erized by blockage of the normal flow	1	1 -	1	1
Fallopian tube stenosis	Asymptomatic clinical or	Symptomatic and intervention	Severe symptoms; elective	Life-threatening consequences;	Death
allopian tube steriosis	diagnostic observations only;	not indicated	operative intervention indicated	urgent operative intervention	Death
	intervention not indicated		'	indicated (e.g., organ resection)	
Definition: A disorder characte	erized by a narrowing of the fallopian	tube lumen.	'	,	•
Female genital tract fistula	Asymptomatic clinical or	Symptomatic and intervention	Severe symptoms; elective	Life-threatening consequences;	Death
ornalo gorinar a doc notala	diagnostic observations only;	not indicated	operative intervention indicated	urgent intervention indicated	Bouiii
	intervention not indicated				
Definition: A disorder characte	erized by an abnormal communication	n between a female reproductive s	ystem organ and another organ o	r anatomic site.	•
Feminization acquired	Mild symptoms; intervention not	1	Í.	_	_
. ommzadon aoganoa	indicated	intervention indicated			
Definition: A disorder characte	erized by the development of seconda	ry female sex characteristics in m	nales due to extrinsic factors.	!	'
Genital edema	Mild swelling or obscuration of	Readily apparent obscuration of	Lymphorrhea; gross deviation	_	_
Jointal Jaonia	anatomic architecture on close	anatomic architecture;	from normal anatomic contour;		
	inspection	obliteration of skin folds; readily	limiting self care ADL		
		apparent deviation from normal			
		anatomic contour			
Definition: A disorder characte	erized by swelling due to an excessive	e accumulation of fluid in the genit	als.		
Gynecomastia	Asymptomatic breast	Symptomatic (e.g., pain or	Severe symptoms; elective	-	-
	enlargement	psychosocial impact)	operative intervention indicated		
Definition: A disorder characte	erized by excessive development of the	ne breasts in males.			
Hematosalpinx	Minimal bleeding identified on	Moderate bleeding; medical	Severe bleeding; transfusion	Life-threatening consequences;	Death
	imaging study or laparoscopy;	intervention indicated	indicated; radiologic or	urgent operative intervention	•
	intervention not indicated		endoscopic intervention	indicated	
	1	1	indicated	1	1

	Rep	roductive system and bi	reast disorders		
			Grade		
Adverse Event	1	2	3	4	5
Definition: A disorder characteri	zed by the presence of blood in a fa	allopian tube.			
rregular menstruation	Intermittent menses with skipped menses for no more than 1 to 3 months	Intermittent menses with skipped menses for more than 4 to 6 months	Persistent amenorrhea for more than 6 months	-	-
Definition: A disorder characteri	zed by irregular cycle or duration of	menses.	Ι	I	I
actation disorder	Mild changes in lactation, not significantly affecting production or expression of breast milk	Changes in lactation, significantly affecting breast production or expression of breast milk	-	-	-
Definition: A disorder characteri	zed by disturbances of milk secretion	on. It is not necessarily related to p	pregnancy that is observed in fema	ales and can be observed in males	S.
Menorrhagia	Mild; iron supplements indicated	Moderate symptoms; medical intervention indicated (e.g., hormones)	Severe; transfusion indicated; surgical intervention indicated (e.g., hysterectomy)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteri	zed by abnormally heavy vaginal bl	eeding during menses.			
Nipple deformity	Asymptomatic; asymmetry with slight retraction and/or thickening of the nipple areolar complex	Symptomatic; asymmetry of nipple areolar complex with moderate retraction and/or thickening of the nipple areolar complex	-	-	-
Definition: A disorder characteri	zed by a malformation of the nipple	•	•		
Oligospermia	Sperm concentration >48 million/mL or motility >68%	Sperm concentration 13 - 48 million/mL or motility 32 - 68%	Sperm concentration <13 million/mL or motility <32%	-	-
Definition: A disorder characteri	zed by a decrease in the number of	spermatozoa in the semen.			
Ovarian hemorrhage	Minimal bleeding identified on imaging study or laproscopy; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteri	zed by bleeding from the ovary.	'	•	'	
Ovarian rupture	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteri	zed by tearing or disruption of the c	varian tissue.	,	•	
Ovulation pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteri ovarian follicle.	zed by marked discomfort sensation	n in one side of the abdomen betw	veen menstrual cycles, around the	time of the discharge of the ovum	from the
Pelvic floor muscle weakness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic, not interfering with bladder, bowel, or vaginal function; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteri	zed by a reduction in the strength o	f the muscles of the pelvic floor.			
Pelvic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteri	zed by marked discomfort sensation	n in the pelvis.			
Penile pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteri	zed by marked discomfort sensation	n in the penis.			1
Perineal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteri	zed by a sensation of marked disco	mfort in the area between the ger	nital organs and the anus.	Γ	
remature menopause	-	-	Present	-	-
Definition: A disorder characteri Prostatic hemorrhage	zed by ovarian failure before the ag Minimal bleeding identified on imaging study; intervention not	e of 40. Symptoms include hot fla Moderate bleeding; medical intervention indicated	shes, night sweats, mood swings a Severe bleeding; transfusion indicated; radiologic or	and a decrease in sex drive. Life-threatening consequences; urgent operative intervention	Death
	indicated		endoscopic intervention indicated	indicated	

Reproductive system and breast disorders							
			Grade		1		
Adverse Event	1	2	3	4	5		
Definition: A disorder characterize	zed by bleeding from the prostate of	gland.	1				
Prostatic obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-		
	zed by compression of the urethra	secondary to enlargement of the p	orostate gland. This results in voidi	ng difficulties (straining to void, sk	ow urine		
stream, and incomplete emptyin	·		0 . 11 .11 .15				
Prostatic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-		
Definition: A disorder characteri:	zed by a sensation of marked disco	omfort in the prostate gland.					
Scrotal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-		
Definition: A disorder characteri:	zed by marked discomfort sensatio	n in the scrotal area.					
Spermatic cord hemorrhage	Minimal bleeding identified on imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder characteri:	zed by bleeding from the spermation	cord.					
Spermatic cord obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-		
Definition: A disorder characteri:	। zed by blockage of the normal flow	of the contents of the spermatic c	1 -	•	1		
Testicular disorder	Asymptomatic; clinical or	Symptomatic but not interfering	Severe symptoms; interfering	Life-threatening consequences;	Death		
	diagnostic observations only;	with urination or sexual	with urination or sexual function;	urgent intervention indicated			
	intervention not indicated	activities; intervention not indicated; limiting instrumental	limiting self care ADL; intervention indicated				
		ADL			l		
	zed by involvement of the testis.	1			L		
Testicular hemorrhage	Minimal bleeding identified on imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder characterize	zed by bleeding from the testis.						
Testicular pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-		
Definition: A disorder characteri:	zed by a sensation of marked disco	omfort in the testis.	'	•			
Uterine fistula	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteri:	zed by an abnormal communication	between the uterus and another	organ or anatomic site.	'	•		
Uterine hemorrhage	Minimal bleeding identified on imaging study; intervention not	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or	Life-threatening consequences; urgent operative intervention	Death		
-	indicated		endoscopic intervention indicated	indicated			
			· ·	indicated			
	indicated zed by bleeding from the uterus. Diagnostic observations only;	Mild symptoms; elective intervention indicated	indicated Severe symptoms; elective	indicated	-		
Definition: A disorder characteriz Uterine obstruction	zed by bleeding from the uterus. Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	indicated	indicated	-		
Definition: A disorder characteri: Uterine obstruction Definition: A disorder characteri:	indicated zed by bleeding from the uterus. Diagnostic observations only;	Mild symptoms; elective intervention indicated et. Moderate pain; limiting	Severe symptoms; elective operative intervention indicated Severe pain; limiting self care	-	-		
Definition: A disorder characteriz Uterine obstruction Definition: A disorder characteriz Uterine pain	indicated zed by bleeding from the uterus. Diagnostic observations only; intervention not indicated zed by blockage of the uterine outle Mild pain	Mild symptoms; elective intervention indicated et. Moderate pain; limiting instrumental ADL	Severe symptoms; elective operative intervention indicated	-	-		
Definition: A disorder characterize Uterine obstruction Definition: A disorder characterize Uterine pain Definition: A disorder characterize Definition: A disorder characte	indicated zed by bleeding from the uterus. Diagnostic observations only; intervention not indicated zed by blockage of the uterine outle Mild pain	Mild symptoms; elective intervention indicated et. Moderate pain; limiting instrumental ADL omfort in the uterus.	Severe symptoms; elective operative intervention indicated Severe pain; limiting self care	-	-		
Definition: A disorder characteriz Uterine obstruction Definition: A disorder characteriz Uterine pain	indicated zed by bleeding from the uterus. Diagnostic observations only; intervention not indicated zed by blockage of the uterine outle Mild pain	Mild symptoms; elective intervention indicated et. Moderate pain; limiting instrumental ADL	Severe symptoms; elective operative intervention indicated Severe pain; limiting self care	-	-		
Definition: A disorder characteriz Uterine obstruction Definition: A disorder characteriz Uterine pain Definition: A disorder characteriz Vaginal discharge	indicated zed by bleeding from the uterus. Diagnostic observations only; intervention not indicated zed by blockage of the uterine outle Mild pain zed by a sensation of marked disco	Mild symptoms; elective intervention indicated et. Moderate pain; limiting instrumental ADL perfort in the uterus. Moderate to heavy vaginal discharge; use of perineal pad or tampon indicated	indicated Severe symptoms; elective operative intervention indicated Severe pain; limiting self care ADL	-			
Definition: A disorder characteriz Uterine obstruction Definition: A disorder characteriz Uterine pain Definition: A disorder characteriz Vaginal discharge	indicated zed by bleeding from the uterus. Diagnostic observations only; intervention not indicated zed by blockage of the uterine outled wild pain zed by a sensation of marked discommiddly and the sensation of marked discommiddly and the sensation of patient)	Mild symptoms; elective intervention indicated et. Moderate pain; limiting instrumental ADL perfort in the uterus. Moderate to heavy vaginal discharge; use of perineal pad or tampon indicated	indicated Severe symptoms; elective operative intervention indicated Severe pain; limiting self care ADL	-	ing years		

	Rep	productive system and b	reast disorders		
			Grade		
Adverse Event	1	2	3	4	5
Vaginal fistula	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by an abnormal communication	between the vagina and another	organ or anatomic site.		
Vaginal hemorrhage	Minimal bleeding identified on clinical exam or imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterize	ed by bleeding from the vagina.				
Vaginal inflammation	Mild discomfort or pain, edema, or redness	Moderate discomfort or pain, edema, or redness; limiting instrumental ADL	Severe discomfort or pain, edema, or redness; limiting self care ADL; small areas of mucosal ulceration	Widespread areas of mucosal ulceration; life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by inflammation involving the v	agina. Symptoms may include red	lness, edema, marked discomfort	and an increase in vaginal dischai	ge.
Vaginal obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterize	ed by blockage of vaginal canal.		1		
Vaginal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterize	ed by a sensation of marked disco	mfort in the vagina.			
Vaginal perforation	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by a rupture in the vaginal wall.				•
Vaginal stricture	Asymptomatic; mild vaginal shortening or narrowing	Vaginal narrowing and/or shortening not interfering with physical examination	Vaginal narrowing and/or shortening interfering with the use of tampons, sexual activity or physical examination	-	Death
Definition: A disorder characterize	ed by a narrowing of the vaginal ca	anal.			_
Vaginismus	Mild discomfort or pain associated with vaginal spasm/tightening; no impact upon sexual function or physical examination	Moderate discomfort or pain associated with vaginal spasm/tightening; disruption in sexual function and physical examination	Severe discomfort or pain associated with vaginal spasm/tightening; unable to tolerate vaginal penetration or physical examination	-	-
Definition: A disorder characterize intercourse.	ed by involuntary spasms of the pe	elvic floor muscles, resulting in pa	thologic tightness of the vaginal w	all during penetration such as duri	ng sexual
Reproductive system and breast disorders - Other, specify		Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

	Respi	ratory, thoracic and med	iastinal disorders					
	Grade							
Adverse Event	1	2	3	4	5			
Adult respiratory distress syndrome	-	-	Present with radiologic findings; intubation not indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death			
Definition: A disorder characteri surgery.	zed by progressive and life-threater	ning pulmonary distress in the abs	ence of an underlying pulmonary	condition, usually following major t	rauma or			
Allergic rhinitis	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-			
	zed by an inflammation of the nasa s of the sinuses, eyes, middle ear, a	•	•	•	ay also			
Apnea	-	-	Present; medical intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death			
Definition: A disorder characteri	<u> </u>							
Aspiration	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Altered eating habits; coughing or choking episodes after eating or swallowing; medical intervention indicated (e.g., suction or oxygen)	Dyspnea and pneumonia symptoms (e.g., aspiration pneumonia); hospitalization indicated; unable to aliment orally	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death			
Definition: A disorder characteri	zed by inhalation of solids or liquids	s into the lungs.	_	_	ı			
Atelectasis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., dyspnea, cough); medical intervention indicated (e.g., chest physiotherapy, suctioning); bronchoscopic suctioning	Oxygen indicated; hospitalization or elective operative intervention indicated (e.g., stent, laser)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death			
Definition: A disorder characteri	zed by the collapse of part or the er	ntire lung.	T	T				
Bronchial fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical management indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death			
Definition: A disorder characteri	zed by an abnormal communication	between the bronchus and anoth	ner organ or anatomic site.					
Bronchial obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., mild wheezing); endoscopic evaluation indicated; radiographic evidence of atelectasis/lobar collapse; medical management indicated (e.g., steroids, bronchodilators)	Shortness of breath with stridor; endoscopic intervention indicated (e.g., laser, stent placement)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death			
Definition: A disorder characteri	zed by blockage of a bronchus pas	sage, most often by bronchial sec	retions and exudates.					
Bronchial stricture	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., rhonchi or wheezing) but without respiratory distress; medical intervention indicated (e.g., steroids, bronchodilators)	Shortness of breath with stridor; endoscopic intervention indicated (e.g., laser, stent placement)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death			
	zed by a narrowing of the bronchial			leg at the second	n			
Bronchopleural fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death			
Definition: A disorder characteri	zed by an abnormal communication	between a bronchus and the plei	ural cavity.	I				
Bronchopulmonary hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g.,	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention	Death			

	Тоорп	ratory, thoracic and med	Grade		
Advance Event	1	2	Grade 3		5
Adverse Event				4	
Bronchospasm	Mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Limiting self care ADL; oxygen saturation decreased	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder charact	terized by a sudden contraction of the	smooth muscles of the bronchial	wall.	1	1
Chylothorax	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thoracentesis or tube drainage indicated	Severe symptoms; elective operative intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder charact	terized by milky pleural effusion (abnor	rmal collection of fluid) resulting fr	om accumulation of lymph fluid in	the pleural cavity.	
Cough	Mild symptoms; nonprescription intervention indicated	Moderate symptoms, medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder charact by a distinctive sound.	terized by sudden, often repetitive, spa	asmodic contraction of the thoraci	c cavity, resulting in violent release	e of air from the lungs and usually a	accompar
Dyspnea	Shortness of breath with moderate exertion	Shortness of breath with minimal exertion; limiting instrumental ADL	Shortness of breath at rest; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder charact	terized by an uncomfortable sensation	of difficulty breathing.			
Epistaxis	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated (e.g., nasal packing, cauterization; topical vasoconstrictors)	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder charact	terized by bleeding from the nose.				
Hiccups	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe symptoms; interfering with sleep; limiting self care ADL	-	-
Definition: A disorder charact	terized by repeated gulp sounds that re	esult from an involuntary opening	and closing of the glottis. This is a	ttributed to a spasm of the diaphra	igm.
Hoarseness	Mild or intermittent voice change; fully understandable; self-resolves	Moderate or persistent voice changes; may require occasional repetition but understandable on telephone; medical evaluation indicated	Severe voice changes including predominantly whispered speech	-	-
Definition: A disorder charact	terized by harsh and raspy voice arisin	g from or spreading to the larynx.	1		
Hypoxia	terized by a decrease in the level of ox	Decreased oxygen saturation with exercise (e.g., pulse oximeter <88%); intermittent supplemental oxygen	Decreased oxygen saturation at rest (e.g., pulse oximeter <88% or PaO2 <=55 mm Hg)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Laryngeal edema	Asymptomatic; clinical or	Symptomatic; medical	Stridor; respiratory distress;	Life-threatening airway	Death
	diagnostic observations only; intervention not indicated	intervention indicated (e.g., dexamethasone, epinephrine, antihistamines)	hospitalization indicated	compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Dean
	terized by swelling due to an excessive			Life threatening	Dog#
Laryngeal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical management indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention indicated (e.g., thoracoplasty, chronic open drainage or multiple thoracotomies)	Death
Definition: A disorder charact	terized by an abnormal communication	between the larynx and another	organ or anatomic site.		
Laryngeal hemorrhage	Mild cough or trace hemoptysis; laryngoscopic findings	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder charact	terized by bleeding from the larynx.	I	1	1	
Laryngeal inflammation	Mild sore throat; raspy voice	Moderate sore throat;	Severe throat pain; endoscopic	1	1

	Respi	ratory, thoracic and med	iastinal disorders		
			Grade		
Adverse Event	1	2	3	4	5
Laryngeal mucositis	Endoscopic findings only; mild discomfort with normal intake	Moderate discomfort; altered oral intake	Severe pain; severely altered eating/swallowing; medical intervention indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characteri	ized by an inflammation involving th	e mucous membrane of the laryn	(.	i .	
Laryngeal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids); limiting instrumental ADL	Limiting self care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteri	ized by blockage of the laryngeal ai	rway.			
Laryngeal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Limiting self care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening consequences; urgent intervention indicated	Death
	ized by a narrowing of the laryngea				L
Laryngopharyngeal dysesthesia	a Mild symptoms; no anxiety; intervention not indicated	Moderate symptoms; mild anxiety, but no dyspnea; short duration of observation and or anxiolytic indicated; limiting instrumental ADL	Severe symptoms; dyspnea and swallowing difficulty; limiting self care ADL	Life-threatening consequences	Death
Definition: A disorder characteri	ized by an uncomfortable persistent	sensation in the area of the laryn	gopharynx.		
Laryngospasm	-	Transient episode; intervention not indicated	Recurrent episodes; noninvasive intervention indicated (e.g., breathing technique, pressure point massage)	Persistent or severe episodes associated with syncope; urgent intervention indicated (e.g., fiberoptic laryngoscopy, intubation, botox injection)	Death
Definition: A disorder characteri	ized by paroxysmal spasmodic mus	cular contraction of the vocal cord		, ,	1
Mediastinal hemorrhage	Radiologic evidence only; minimal symptoms; intervention not indicated	Moderate symptoms; medical	Transfusion, radiologic, endoscopic, or elective operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteri	ized by bleeding from the mediastin	um.	1 '	l	1
Nasal congestion	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Associated with bloody nasal discharge or epistaxis	-	-
	ized by obstruction of the nasal pas	1			
Pharyngeal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteri	ized by an abnormal communication	n between the pharynx and anothe	er organ or anatomic site.	T	
Pharyngeal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characteri	ized by bleeding from the pharynx.	T		T	
Pharyngeal mucositis	Endoscopic findings only; minimal symptoms with normal oral intake; mild pain but analgesics not indicated	Moderate pain and analgesics indicated; altered oral intake; limiting instrumental ADL	Severe pain; unable to adequately aliment or hydrate orally; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteri	zed by an inflammation involving th	e mucous membrane of the phary	nx.		
Pharyngeal necrosis	-	-	Inability to aliment adequately by GI tract; tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death

	Respir	ratory, thoracic and med	lastinal disorders		
			Grade		
Adverse Event	1	2	3	4	5
Definition: A disorder character	rized by a necrotic process occurring	in the pharynx.	<u> </u>		
Pharyngeal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids); limiting instrumental ADL	Limiting self care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder character	rized by a narrowing of the pharynge	al airway.	'	'	'
Pharyngolaryngeal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder character	rized by marked discomfort sensation	n in the pharyngolaryngeal region.			
Pleural effusion	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; intervention indicated (e.g., diuretics or limited therapeutic thoracentesis)	Symptomatic with respiratory distress and hypoxia; surgical intervention including chest tube or pleurodesis indicated	indicated	Death
Definition: A disorder character	rized by an increase in amounts of flo	uid within the pleural cavity. Symp	toms include shortness of breath,	cough and marked chest discomfo	ort.
Pleural hemorrhage	Asymptomatic; mild hemorrhage confirmed by thoracentesis	Symptomatic or associated with pneumothorax; chest tube drainage indicated	>1000 ml of blood evacuated; persistent bleeding (150-200 ml/hr for 2 - 4 hr); persistent transfusion indicated; elective operative intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder character	rized by bleeding from the pleural ca	vity.	•		•
Pleuritic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder character	rized by marked discomfort sensation	n in the pleura.	T	T	
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
	rized by inflammation focally or diffus				L
Pneumothorax	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; intervention indicated (e.g., tube placement without sclerosis)	Sclerosis and/or operative intervention indicated; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder character	rized by abnormal presence of air in	the pleural cavity resulting in the	collapse of the lung.		
Postnasal drip	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder character	rized by excessive mucous secretion	in the back of the nasal cavity or	throat, causing sore throat and/or	coughing.	
Productive cough		Moderate sputum production; limiting instrumental ADL	Persistent or copious production of sputum; limiting self care ADL	-	-
	rized by expectorated secretions upo		0		D4h
Pulmonary edema	Radiologic findings only; minimal dyspnea on exertion	Moderate dyspnea on exertion; medical intervention indicated; limiting instrumental ADL	Severe dyspnea or dyspnea at rest; oxygen indicated; limiting self care ADL	Life-threatening respiratory compromise; urgent intervention or intubation with ventilatory support indicated	Death
Definition: A disorder character	rized by accumulation of fluid in the I		nce of the gas exchange that may	lead to respiratory failure.	1
Pulmonary fibrosis	Mild hypoxemia; radiologic pulmonary fibrosis <25% of lung volume	Moderate hypoxemia; evidence of pulmonary hypertension; radiographic pulmonary fibrosis 25 - 50%	Severe hypoxemia; evidence of right-sided heart failure; radiographic pulmonary fibrosis >50 - 75%	Life-threatening consequences (e.g., hemodynamic/pulmonary complications); intubation with ventilatory support indicated; radiographic pulmonary fibrosis >75% with severe honeycombing	Death
Definition: A disorder character	rized by the replacement of the lung	tissue by connective tissue, leading	ng to progressive dyspnea, respira	tory failure or right heart failure.	
Pulmonary fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical management indicated; limiting instrumental ADL	Limiting self care ADL; endoscopic stenting or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death

	Respi	ratory, thoracic and med						
	Grade							
Adverse Event	1	2	3	4	5			
	zed by an abnormal communication			ler u	.			
Pulmonary hypertension	Minimal dyspnea; findings on physical exam or other	Moderate dyspnea, cough; requiring evaluation by cardiac	Severe symptoms, associated with hypoxemia, right heart	Life-threatening airway consequences; urgent	Death			
	evaluation	catheterization and medical intervention	failure; oxygen indicated	intervention indicated (e.g., tracheotomy or intubation)				
Definition: A disorder characteriz	zed by an increase in pressure with	in the pulmonary circulation due to	o lung or heart disorder.		•			
Respiratory failure	-	-	-	Life-threatening consequences; urgent intervention, intubation,	Death			
				or ventilatory support indicated				
Definition: A disorder characteriz with an increase in arterial levels	zed by impaired gas exchange by t s of carbon dioxide.	he respiratory system resulting in	hypoxemia and a decrease in oxy	genation of the tissues that may be	e associat			
Retinoic acid syndrome	Fluid retention; <3 kg of weight	Moderate signs or symptoms;	Severe symptoms;	Life-threatening consequences;	Death			
Council of the Counci	gain; intervention with fluid restriction and/or diuretics indicated	steroids indicated	hospitalization indicated	ventilatory support indicated	Boun			
Definition: A disorder characteriz	zed by weight gain, dyspnea, pleur	l al and pericardial effusions, leukod	l cytosis and/or renal failure original	I ly described in patients treated wit	l th all-trans			
Sinus disorder	Asymptomatic mucosal crusting;	1 * '	Stenosis with significant nasal	Necrosis of soft tissue or bone;	Death			
	blood-tinged secretions	edema/narrowing interfering with airflow; limiting instrumental ADL	obstruction; limiting self care ADL	urgent operative intervention indicated				
Definition: A disorder characteriz	। zed by involvement of the paranasa	ı		I				
Sleep apnea	Snoring and nocturnal sleep	Moderate apnea and oxygen	Oxygen desaturation;	Cardiovascular or	Death			
	arousal without apneic periods	desaturation; excessive daytime sleepiness; medical evaluation	associated with hypertension; medical intervention indicated;	neuropsychiatric symptoms; urgent operative intervention				
		indicated; limiting instrumental ADL	limiting self care ADL	indicated				
Definition: A disorder characteriz	zed by cessation of breathing for sh	nort periods during sleep.	!					
Sneezing	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-			
Definition: A disorder characteriz	zed by the involuntary expulsion of	air from the nose.						
Sore throat	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL; limiting ability to swallow	-	-			
Definition: A disorder characteriz	। zed by of marked discomfort in the	ı	·,g,	I	Į.			
Stridor	-	-	Respiratory distress limiting self	Life-threatening airway	Death			
			care ADL; medical intervention indicated	compromise; urgent intervention indicated (e.g., tracheotomy or				
				intubation)				
Definition: A disorder characteriz	zed by a high pitched breathing sou	und due to laryngeal or upper airw	ay obstruction.	Ť .				
Tracheal fistula	Asymptomatic; clinical or	Symptomatic; tube	Severe symptoms; limiting self	Life-threatening consequences;	Death			
	diagnostic observations only; intervention not indicated	thoracostomy or medical intervention indicated; limiting	care ADL; endoscopic or operative intervention indicated	urgent operative intervention indicated (e.g., thoracoplasty,				
		instrumental ADL	(e.g., stent or primary closure)	chronic open drainage or multiple thoracotomies)				
Definition: A disorder characteriz	। zed by an abnormal communicatior	l between the trachea and anothe	I r organ or anatomic site.	Imalapie aloracotomico)				
Tracheal mucositis	Endoscopic findings only;	Moderate symptoms; medical	Severe pain; hemorrhage or	Life-threatening consequences;	Death			
	minimal hemoptysis, pain, or	intervention indicated; limiting	respiratory symptoms; limiting	urgent intervention indicated				
Definition: A disorder characteris	respiratory symptoms	instrumental ADL	self care ADL	I	I			
Definition: A disorder characteriz	zed by an inflammation involving the Asymptomatic; clinical or	Symptomatic (e.g., noisy airway	ea. Stridor or respiratory distress	Life-threatening airway	Death			
Hacheal Stellosis	diagnostic observations only;	breathing), but causing no	limiting self care ADL;	compromise; urgent intervention	Deam			
	intervention not indicated	respiratory distress; medical	endoscopic intervention	indicated (e.g., tracheotomy or				
		management indicated (e.g., steroids)	indicated (e.g., stent, laser)	intubation)				
Definition: A disorder characterize	zed by a narrowing of the trachea.							

	Respi	ratory, thoracic and med	iastinal disorders			
	Grade					
Adverse Event	1	2	3	4	5	
Voice alteration	Mild or intermittent change from normal voice	Moderate or persistent change from normal voice; still understandable	Severe voice changes including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; may require assistive technology	-	-	
Definition: A disorder characteriz	ed by a change in the sound and/o	or speed of the voice.				
Wheezing	Detectable airway noise with minimal symptoms	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe respiratory symptoms limiting self care ADL; oxygen therapy or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characteriz	ed by a high-pitched, whistling sou	ind during breathing. It results from	n the narrowing or obstruction of t	he respiratory airways.		
Respiratory, thoracic and mediastinal disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	

	J.	in and subcutaneous tis				
	Grade					
Adverse Event	1	2	3	4	5	
Alopecia	Hair loss of <50% of normal for	Hair loss of >=50% normal for	-	-	-	
	that individual that is not	that individual that is readily				
	obvious from a distance but only	apparent to others; a wig or hair				
	on close inspection; a different	piece is necessary if the patient				
	hair style may be required to	desires to completely				
	cover the hair loss but it does	camouflage the hair loss;				
	not require a wig or hair piece to	associated with psychosocial				
	camouflage	impact				
Definition: A disorder characteriz	zed by a decrease in density of hair	r compared to normal for a given i	ndividual at a given age and body	location.		
Body odor	Mild odor; physician intervention	Pronounced odor; psychosocial	-	-	-	
	not indicated; self care	impact; patient seeks medical				
	interventions	intervention				
Definition: A disorder characteriz	zed by an abnormal body smell res	ulting from the growth of bacteria	on the body.	ı	'	
Bullous dermatitis	Asymptomatic; blisters covering	Blisters covering 10 - 30% BSA;	Blisters covering >30% BSA;	Blisters covering >30% BSA;	Death	
	<10% BSA	painful blisters; limiting	limiting self care ADL	associated with fluid or		
		instrumental ADL	and ADE	electrolyte abnormalities; ICU		
		Institutional ADL		care or burn unit indicated		
D-G-iti A di ! ! : !			I a college and filled to the first	Poare or burn unit indicated	I	
	zed by inflammation of the skin cha					
Dry skin	Covering <10% BSA and no	Covering 10 - 30% BSA and	Covering >30% BSA and	-	-	
	associated erythema or pruritus	associated with erythema or	associated with pruritus; limiting			
		pruritus; limiting instrumental	self care ADL			
		ADL				
Definition: A disorder characteriz	zed by flaky and dull skin; the pores	s are generally fine, the texture is	a papery thin texture.			
Erythema multiforme	Target lesions covering <10%	Target lesions covering 10 -	Target lesions covering >30%	Target lesions covering >30%	Death	
,	BSA and not associated with	30% BSA and associated with	BSA and associated with oral or	BSA; associated with fluid or		
	skin tenderness	skin tenderness	genital erosions	electrolyte abnormalities; ICU		
	Simil torragings	January 1970	gorman or obtains	care or burn unit indicated		
Definition: A disorder characteriz	ा zed by target lesions (a pink-red rin	ır around a nale center)	1	l	1	
Erythroderma	lea by tanger recience (a print rea int	Erythema covering >90% BSA	Erythema covering >90% BSA	Erythema covering >90% BSA	Death	
Erythodenna	-	without associated symptoms;	•	with associated fluid or	Dealii	
		1	with associated symptoms (e.g.,			
		limiting instrumental ADL	pruritus or tenderness); limiting	electrolyte abnormalities; ICU		
			self care ADL	care or burn unit indicated		
Definition: A disorder characteriz	zed by generalized inflammatory er	ythema and exfoliation. The inflan	nmatory process involves > 90% o	f the body surface area.		
Fat atrophy	Covering <10% BSA and	Covering 10 - 30% BSA and	Covering >30% BSA;	-	-	
	asymptomatic	associated with erythema or	associated with erythema or			
		tenderness; limiting instrumental	tenderness; limiting self-care			
		ADL	ADL			
Definition: A disorder characteriz	zed by shrinking of adipose tissue.					
Hirsutism	In women, increase in length,	In women, increase in length,	-	-	-	
	thickness or density of hair in a	thickness or density of hair in a				
	male distribution that the patient	-				
	is able to camouflage by	daily shaving or consistent				
	periodic shaving, bleaching, or	destructive means of hair				
	removal of hair	removal to camouflage;				
		associated with psychosocial				
		impact				
Definition: A disorder characterize	Ized by the presence of excess hair		ı s where growth is considered to b	। e a secondary male characteristic	ı and und	
androgen control (beard, mousta		g a Homes in anatomic site		ondications	unu	
Hyperhidrosis	Limited to one site (palms,	Involving >1 site; patient seeks	Generalized involving sites	_	1_	
турстпигозіз	" "		-	-	1	
	soles, or axillae); self care interventions	medical intervention; associated	other than palms, soles, or			
	TITLETVENTIONS	with psychosocial impact	axillae; associated with	I	1	
	miles verifierie					
			electrolyte/hemodynamic imbalance			

		in and subcutaneous tis	Grade		
A d	4	2	Grade 3	4	5
Adverse Event Hypertrichosis	Increase in length, thickness or density of hair that the patient is either able to camouflage by periodic shaving or removal of hairs or is not concerned enough about the overgrowth to use any form of hair removal	Increase in length, thickness or density of hair at least on the usual exposed areas of the body [face (not limited to beard/moustache area) plus/minus arms] that requires frequent shaving or use of	-	-	-
Definition: A disorder characteri.	zed by hair density or length beyon	destructive means of hair removal to camouflage; associated with psychosocial impact	a particular body region, for a part	icular age or race.	
Hypohidrosis	-	Symptomatic; limiting instrumental ADL	Increase in body temperature; limiting self care ADL	Heat stroke	Death
Definition: A disorder characteri.	zed by reduced sweating.	T	T	T	1
Lipohypertrophy	Asymptomatic and covering <10% BSA	Covering 10 - 30% BSA and associated tenderness; limiting instrumental ADL	Covering >30% BSA and associated tenderness and narcotics or NSAIDs indicated; lipohypertrophy; limiting self care ADL	-	-
Definition: A disorder characteri.	zed by hypertrophy of the subcutan	eous adipose tissue at the site of	multiple subcutaneous injections of	of insulin.	
Nail discoloration	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
	zed by a change in the color of the				T
Nail Ioss	Asymptomatic separation of the nail bed from the nail plate or nail loss	Symptomatic separation of the nail bed from the nail plate or nail loss; limiting instrumental ADL	-	-	-
Definition: A disorder characteri	zed by loss of all or a portion of the	nail.	_		
Nail ridging	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characteriz	zed by vertical or horizontal ridges	on the nails.			
Pain of skin	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterize	zed by marked discomfort sensation	n in the skin.	T	T	
Palmar-plantar erythrodysesthesia syndrome	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain zed by redness, marked discomfort	Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL	Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self care ADL		-
	1			eet.	
Periorbital edema	Soft or non-pitting	Indurated or pitting edema; topical intervention indicated	Edema associated with visual disturbance; increased intraocular pressure, glaucoma or retinal hemorrhage; optic neuritis; diuretics indicated; operative intervention indicated		-
Definition: A disorder characteri	zed by swelling due to an excessive	e accumulation of fluid around the	orbits of the face.	1	
Photosensitivity	Painless erythema and erythema covering <10% BSA	Tender erythema covering 10 - 30% BSA	Erythema covering >30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (e.g., narcotics or NSAIDs)	Life-threatening consequences; urgent intervention indicated	Death

Skin and subcutaneous tissue disorders					
			Grade		1
Adverse Event	1	2	3	4	5
Pruritus	Mild or localized; topical intervention indicated	Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated;	Intense or widespread; constant; limiting self care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated	-	-
		limiting instrumental ADL			
Definition: A disorder character	ized by an intense itching sensation	•			
Purpura	Combined area of lesions covering <10% BSA	Combined area of lesions covering 10 - 30% BSA; bleeding with trauma	Combined area of lesions covering >30% BSA; spontaneous bleeding	-	-
	ized by hemorrhagic areas of the sk	in and mucous membrane. Newe	r lesions appear reddish in color. C	Older lesions are usually a darker	purple color
and eventually become a browr	T .				
Rash acneiform	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; lifethreatening consequences	Death
Definition: A disorder character	ized by an eruption of papules and p	oustules, typically appearing in fac	ce, scalp, upper chest and back.		
Rash maculo-papular	Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering >30% BSA with or without associated symptoms; limiting self care ADL	-	-
	ized by the presence of macules (fla		nown as morbillform rash, it is one	of the most common cutaneous a	dverse
events, frequently affecting the Scalp pain	upper trunk, spreading centripetally Mild pain	Moderate pain; limiting	Severe pain; limiting self care	-	-
		instrumental ADL	ADL		
Definition: A disorder character	ized by marked discomfort sensation	n in the skin covering the top and	the back of the head.	1	
Skin atrophy	Covering <10% BSA; associated with telangiectasias or changes in skin color	Covering 10 - 30% BSA; associated with striae or adnexal structure loss	Covering >30% BSA; associated with ulceration	-	-
Definition: A disorder character	ized by the degeneration and thinning	ng of the epidermis and dermis.			
Skin hyperpigmentation	Hyperpigmentation covering <10% BSA; no psychosocial impact	Hyperpigmentation covering >10% BSA; associated psychosocial impact	-	-	-
Definition: A disorder character	ized by darkening of the skin due to	excessive melanin deposition.	1		
Skin hypopigmentation	Hypopigmentation or depigmentation covering <10% BSA; no psychosocial impact	Hypopigmentation or depigmentation covering >10% BSA; associated psychosocial impact	-	-	-
Definition: A disorder character	ized by loss of skin pigment.				
Skin induration	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration, unable to slide or pinch skin; limiting joint movement or orifice (e.g., mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death
Definition: A disorder character	ized by an area of hardness in the s	kin.	1		
Skin ulceration	Combined area of ulcers <1 cm; nonblanchable erythema of	Combined area of ulcers 1 - 2 cm; partial thickness skin loss	Combined area of ulcers >2 cm; full-thickness skin loss involving	Any size ulcer with extensive destruction, tissue necrosis, or	Death

	Sk	in and subcutaneous tis	sue disorders		
			Grade		
Adverse Event	1	2	3	4	5
Stevens-Johnson syndrome	-	-	Skin sloughing covering <10% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment)	Skin sloughing covering 10 - 30% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment)	Death
Definition: A disorder characterize mucous membranes.	ed by less than 10% total body ski	n area separation of dermis. The	syndrome is thought to be a hyper	rsensitivity complex affecting the s	kin and the
Telangiectasia	Telangiectasias covering <10% BSA	Telangiectasias covering >10% BSA; associated with psychosocial impact	-	-	-
Definition: A disorder characterize	ed by local dilatation of small vess	els resulting in red discoloration o	f the skin or mucous membranes.	1	
Toxic epidermal necrolysis	-	-	-	Skin sloughing covering >=30% BSA with associated symptoms (e.g., erythema, purpura, or epidermal detachment)	Death
Definition: A disorder characterize mucous membranes.	ed by greater than 30% total body	skin area separation of dermis. T	he syndrome is thought to be a hy	persensitivity complex affecting th	e skin and the
Urticaria	Urticarial lesions covering <10% BSA; topical intervention indicated	Urticarial lesions covering 10 - 30% BSA; oral intervention indicated	Urticarial lesions covering >30% BSA; IV intervention indicated	-	-
Definition: A disorder characterize	ed by an itchy skin eruption charac	cterized by wheals with pale interio	ors and well-defined red margins.		
Skin and subcutaneous tissue disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Social circumstances							
		Grade					
Adverse Event	1	1 2 3 4					
Menopause	Menopause occurring at age 46 - 53 years of age	Menopause occurring at age 40 - 45 years of age	Menopause occurring before age 40 years of age	-	-		
Definition: A disorder characteriz	ed by the permanent cessation of	menses, usually defined by 12 co	nsecutive months of amenorrhea i	n a woman over 45 years of age.			
Social circumstances - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated;	Life-threatening consequences; urgent intervention indicated	Death		
			disabling; limiting self care ADL				

Surgical and medical procedures						
	Grade					
Adverse Event	1	2	3	4	5	
Surgical and medical	Asymptomatic or mild	Moderate; minimal, local or	Severe or medically significant	Life-threatening consequences;	Death	
procedures - Other, specify	symptoms; clinical or diagnostic	noninvasive intervention	but not immediately life-	urgent intervention indicated		
	observations only; intervention	indicated; limiting age-	threatening; hospitalization or			
	not indicated	appropriate instrumental ADL	prolongation of existing			
			hospitalization indicated;			
1			disabling; limiting self care ADL			

		Vascular disord	ers		
			Grade		
Adverse Event	1	2	3	4	5
Capillary leak syndrome	-	Symptomatic; medical intervention indicated	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	rized by leakage of intravascular flui ck syndromes, low-flow states, ische	·		•	
Flushing	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Symptomatic, associated with hypotension and/or tachycardia; limiting self care ADL	-	-
Definition: A disorder characte	rized by episodic reddening of the fa	ice.			
Hematoma	Mild symptoms; intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	rized by a localized collection of bloc	od, usually clotted, in an organ, sp	ace, or tissue, due to a break in th	e wall of a blood vessel.	
Hot flashes	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characte	rized by an uncomfortable and temp	orary sensation of intense body w	armth, flushing, sometimes accom	panied by sweating upon cooling.	
Hypertension	Prehypertension (systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg)	Stage 1 hypertension (systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg); medical intervention indicated; recurrent or persistent (>=24 hrs); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg if previously	Stage 2 hypertension (systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated Pediatric: Same as adult	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated Pediatric: Same as adult	Death
Definition: A disorder characte	rized by a pathological increase in b	WNL; monotherapy indicated Pediatric: recurrent or persistent (>=24 hrs) BP >ULN; monotherapy indicated lood pressure; a repeatedly elevat	ion in the blood pressure exceedir	ng 140 over 90 mm Hg.	
Hypotension	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention or hospitalization indicated	Life-threatening and urgent intervention indicated	Death
Definition: A disorder characte	rized by a blood pressure that is belo	ow the normal expected for an ind	ividual in a given environment.		
Lymph leakage	-	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	rized by the loss of lymph fluid into t		Ĺ		1
Lymphedema	Trace thickening or faint discoloration	Marked discoloration; leathery skin texture; papillary formation; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characte	rized by excessive fluid collection in	tissues that causes swelling.			
Lymphocele	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	-	-
Definition: A disorder characte	rized by a cystic lesion containing ly	mph.			
Peripheral ischemia	-	Brief (<24 hrs) episode of ischemia managed non- surgically and without permanent deficit	Recurring or prolonged (>=24 hrs) and/or invasive intervention indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A disorder characte	rized by impaired circulation to an ex	ktremity.	1	1	
Phlebitis	-	Present	-	-	-
Definition: A disorder characte	rized by inflammation of the wall of a	a vein.		_	
Superficial thrombophlebitis	-	Present	-	-	-
Definition: A disorder characte	rized by a blood clot and inflammation	on involving a superficial vein of th	e extremities.		

		Vascular disord	ers		
			Grade		
Adverse Event	1	2	3	4	5
Superior vena cava syndrome	Asymptomatic; incidental finding of SVC thrombosis	Symptomatic; medical intervention indicated (e.g., anticoagulation, radiation or chemotherapy)	Severe symptoms; multi- modality intervention indicated (e.g., anticoagulation, chemotherapy, radiation, stenting)	Life-threatening consequences; urgent multi-modality intervention indicated (e.g., lysis, thrombectomy, surgery)	Death
Definition: A disorder characteriz	ed by obstruction of the blood flow	in the superior vena cava. Signs	and symptoms include swelling an	d cyanosis of the face, neck, and	upper arms,
cough, orthopnea and headache				.	
Thromboembolic event	Venous thrombosis (e.g., superficial thrombosis)	Venous thrombosis (e.g., uncomplicated deep vein thrombosis), medical intervention indicated	Thrombosis (e.g., uncomplicated pulmonary embolism [venous], non-embolic cardiac mural [arterial] thrombus), medical intervention indicated	Life-threatening (e.g., pulmonary embolism, cerebrovascular event, arterial insufficiency); hemodynamic or neurologic instability; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by occlusion of a vessel by a th	rombus that has migrated from a	distal site via the blood stream.		
Vasculitis	Asymptomatic, intervention not indicated	Moderate symptoms, medical intervention indicated	Severe symptoms, medical intervention indicated (e.g., steroids)	Life-threatening; evidence of peripheral or visceral ischemia; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by inflammation involving the w	rall of a vessel.	•		
Visceral arterial ischemia	-	Brief (<24 hrs) episode of ischemia managed medically and without permanent deficit	Prolonged (>=24 hrs) or recurring symptoms and/or invasive intervention indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A disorder characteriz	ed by a decrease in blood supply o	due to narrowing or blockage of a	visceral (mesenteric) artery.		
Vascular disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death







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Appendix B: Pemphigus Disease Area Index

- Skin	- Activity	- Damage	
Anatomical	Erosion / Blisters or new erythema		Post-inflammatory hyperpigmentation or
Location	•	Normale and	erythema from resolving lesion
	0 absent 1 1-3 lesions up to one > 2 cm in any diameter, none	Number	0 absent
	1 ,	lesions if 3	1 present
	> 6 cm		
	2 2-3 lesions, at least two > 2 cm diameter, none > 6		
	cm 3 > 3 lesions, none > 6 cm diameter		
Ears	diameter or entire area		
Nose			
Rest of the face			
Neck			
Chest			
Abdomen			
Back, buttocks			
Arms			
Hands			
Legs			
Feet			
Genitals	//20		/10
Total skin	/120		/12
- Scalp			
Scalp	Erosion/Blisters or new erythema	Number	Post-inflammatory hyperpigmentation or
•	0 1	lesions if 3	erythema from resolving lesion
	0 absent		0 absent
	1 in one quadrant		1 present
	2 two quadrants 3 three quadrants		
	3 three quadrants 4 affects whole skull		
T-4-1 C1- (0.10)	10 at least one lesion > 6 cm		/1
Total Scalp (0-10) Mucous membran	/10		/1
Anatomical	e I	ı	1
location	Erosion/Blisters		
location	0 1	NI1	
	0 absent 1 1 lesion	Number	
		lesions	
	2 2-3 lesions 5 > 3 lesions or 2 lesions > 2 cm	if 3	
	10 entire area		
Evec	10 Chine area		
Eyes Nose			
Buccal mucosa			
Hard palate			
Soft palate			
Upper gingiva			
Lower gingiva			
Tongue			
Floor of mouth			
Labial bucosa			
Posterior pharynx			
Anogenital	/120		
Total Mucosa	/120		

Syntimmune, Inc.

CLINICAL STUDY PROTOCOL

A Phase 1b, Multicenter, Open-Label, Safety, Tolerability, and Activity Study of SYNT001 in Subjects with Chronic Pemphigus (Vulgaris or Foliaceus)

Protocol Number: SYNT001-103

IND Number: 132727

Study Drug: SYNT001

Sponsor: Syntimmune, Inc.

257 Park Avenue South

15th Floor

New York, NY 10010

Medical Monitor: PPD

43 Thorndike Street, Cambridge, MA 01240

Phone: PPD extension PPD

Mobile: PPD

Original Protocol: 18 January 2017 **Amendment 1.1:** 21 March 2017

Confidentiality Statement

The information contained herein is confidential and the proprietary property of Syntimmune, Inc. and any unauthorized use or disclosure of such information without the prior written authorization of Syntimmune is expressly prohibited.

SPONSOR SIGNATURE

I have read and approve this protocol. My signature, in conjunction with the signature of the Investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonisation Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), and the ethical principles that have their origins in the Declaration of Helsinki.

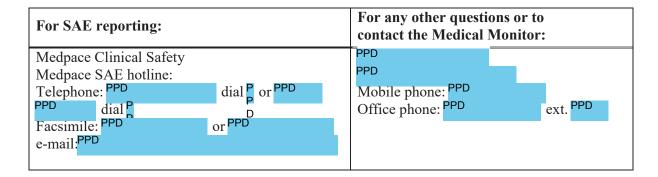
PPU	
	March 21, 2017
	Date of Signature (DD Mm YYYY)

PROCEDURES IN CASE OF EMERGENCY

Serious Adverse Events

Any death, serious adverse event (SAE)* occurring in a subject while receiving study drug or within 7 days of receiving study drug, even though the event may not appear to be study drug related, must be promptly reported (within 24 hours) by telephone or electronic communication to the sponsor (or designee).

Emergency Contact Information



SAE CRITERIA

- * A <u>serious adverse event</u> (SAE) is any untoward medical occurrence that at any dose results in any of the following outcomes, regardless of relationship to study drug (see Section 11.3.1, Serious Adverse Events for additional information):
 - Death
 - Life-threatening adverse drug event
 - Inpatient hospitalization or prolongation of existing hospitalization
 - A persistent or significant disability/ incapacity
 - A congenital anomaly/birth defect
 - An important medical event that may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Syntimmune, Inc.

Protocol SYNT001-103

INVESTIGATOR SIGNATURE

I have read and approve this protocol. My signature, in conjunction with the signature of the sponsor, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonization Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), and the ethical principles that have their origins in the Declaration of Helsinki.

Nothing in this document is intended to limit the authority of a physician to provide emergency

medical care under applicable regulations.	
Investigator Signature	Date of Signature (DD Mm YYYY)
Name of Investigator (please print)	

1 SYNOPSIS

Study title	A Phase 1b, Multicenter, Open-Label, Safety, Tolerability, and Activity Study of SYNT001 in Subjects with Chronic Pemphigus (Vulgaris or Foliaceus)					
Protocol number	SYNT001-103					
Number of study centers	Approximately 10 (US)					
Clinical phase	Phase 1b					
Study background	SYNT001, a humanized, affinity-matured IgG4-kappa monoclonal antibody (mAb), blocks IgG and IgG immune complex (IC) interactions with the neonatal Fc receptor (FcRn) and thereby the major functions of FcRn in protecting IgG and IgG immune complexes from degradation and their role in downstream signaling events. Specific and high affinity blockade of FcRn with SYNT001 has been shown to increase the catabolism of IgG and IgG IC in healthy volunteers. This predicts that SYNT001 will also accelerate degradation of endogenous circulating IgG autoantibodies and IgG-antigen IC specifically involved in the pathogenesis of autoimmunity. Blocking FcRn interactions with IgG containing immune complexes further predicts that SYNT001 will have consequences for innate and adaptive cellular immunity. In the first instance, blocking multimeric IgG IC interactions with FcRn within antigen presenting cells will result in inhibition of IC-stimulated inflammatory cytokine production and release by these cells. In addition, as FcRn determines the intracellular itinerary of IgG immune complexes within and among compartments important in cellular immunity, it is further anticipated that SYNT001 will block antigen processing and presentation of antigens contained within IC that otherwise lead to CD8+ and CD4+T cell activation. Thus, SYNT001 will specifically target immune functions associated with IgG and IC that are involved in many autoimmune conditions and dismantle their ability to cause disease. SYNT001 targets mechanisms contributing to pathology in a variety of IgG-mediated autoimmune disorders, including warm antibody autoimmune hemolytic anemia (WAIHA), pemphigus, and chronic inflammatory demyelinating polyneuropathy (CIDP). While current treatments for certain autoimmune disorders including chronic steroids, immunosuppressants, intravenous immunoglobulin (IVIG), plasmapheresis, and anti-CD20 monoclonal antibodies (mAbs), such as rituximab, can be effective, they are frequently associated with significant adverse effects, an					

	pathogenic role in the mucosal and cutaneous manifestations in patients with pemphigus. Administration of SYNT001, leading to a significant decrease in total IgG, and thereby a corresponding decrease in the level of the pathogenic autoantibodies as well as the ICs to which they are associated, should lead to a decrease in the mucosal and cutaneous manifestations in subjects with pemphigus. Moreover, the ability of SYNT001 to reduce circulating immune complexes (CICs) and the associated innate and adaptive immune responses may allow for further sustained disease modification.						
Study rationale	This study is being conducted to further evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity of intravenous (IV) SYNT001 as well as its effects on pemphigus disease activity markers.						
Study objectives	Primary objective						
	To evaluate the safety and tolerability of 5 once-weekly IV infusions of SYNT001 at different dose levels in subjects with chronic pemphigus (vulgaris or foliaceus)						
	Secondary objectives						
	 To determine the PK of SYNT001 following 5 once-weekly 1-hour IV infusions at different dose levels To assess the effect of 5 once-weekly doses of SYNT001 at different dose levels on the following PD biomarkers: Immunoglobulins: IgG, IgG subtypes (IgG1-4), IgA, IgM Albumin 						
	 Albumin To assess the effect of 5 once-weekly doses of SYNT001 at different dose levels on the following disease activity markers: 						
	 Serum anti-desmoglein (Dsg) (1 and 3) antibody levels 						
	o Pemphigus Disease Area Index (PDAI)						
	To assess immunogenicity (anti-SYNT001 antibodies)						
	Exploratory objectives						
	• To assess the effect of 5 once-weekly doses of SYNT001 at different dose levels on the following biomarkers, including:						
	 Serum anti-epithelial cell antibody (AECA) levels by indirect immunofluorescence 						
	o Circulating immune complexes (CIC)						
	o Complement component 3 (C3)						
	 Exploratory biomarkers (FCGR2A (single nucleotide polymorphism- SNP), RNAseq, urine IgG) 						

0	Immune phenotyping by flow cytometry for CD3 ⁺ CD4 ⁺ T,
	CD3 ⁺ CD8 ⁺ T, monocytes, NK cells and B cells
0	SYNT001 levels in skin bionsies (ontional)

- O SYNT001 levels in skin biopsies (optional)
- To characterize corticosteroid use during the study

Study design

Phase 1b, multicenter, open-label, safety, tolerability, and activity study

Methodology

Two cohorts of 8 eligible subjects each will receive 5 once-weekly 60-minute infusions of SYNT001 in planned doses of 10 mg/kg or 30 mg/kg. Based on review of safety, PD, and clinical outcomes of these 2 cohorts, a third cohort of up to 8 subjects may be treated at another dose, with a maximum dose of 45 mg/kg, but may also be lower than 10 mg/kg or between 10 and 30 mg/kg, inclusive.

Cohort	No. of subjects	Dose
1	8	SYNT001 10 mg/kg
2	8	SYNT001 30 mg/kg

Cohorts will be dosed sequentially beginning with Cohort 1. The first 2 subjects will be dosed at least 24 hours apart. A review of the 24-hour safety data for the first subject will be performed to ensure that there are no overt safety concerns before dosing the second subject. A review of the 7-day safety data for the first 2 subjects will be performed prior to dosing the remaining 6 subjects in the cohort. This evaluation will include a review of AE/SAE reports, vital sign assessments, physical examinations, ECGs, and clinical laboratory testing. The seriousness, severity, and relatedness of AEs/SAEs will also be considered in the safety evaluation. Safety data will be reviewed on a continuous basis throughout the study. All safety data and any available and relevant PD data through Day 42 (2 weeks after the last subject's last dose in Cohort 1) will be reviewed by a dose escalation committee before Cohort 2 is initiated. Escalation to Cohort 2 will proceed if there are no concerning safety signals and the review of available and relevant PD data supports advancing to a higher dose. The dose for Cohort 2 will be finalized after review of the safety and PD data, but will not exceed 30 mg/kg. Cohort 2 and Cohort 3, if added, will be dosed per the same schedule as Cohort 1.

On days where study drug is administered, vital sign and pulse oximetry measurements will be collected immediately prior to the infusion; 15, 30, and 45 minutes after the start of the infusion; at completion of the infusion; and 30 minutes, 1 hour and 2 hours following completion of the infusion.

On Days 0 and 28, PK blood samples will be collected prior to infusion start and then over the subsequent 48 hours. Subjects will remain at the clinic through the 6-hour PK sample collection and will return to the clinic for the 24- and 48-hour collections. Additional samples will be collected on Days 5 and 33.

On Day 0 photographs will be taken of active lesions. Follow-up photographs will be taken of the same areas on Days 33 and 56. If a subject begins a steroid taper, additional photographs will be taken at the clinic visit during which the decision to begin the taper is made.

Subsequent visits will occur on Days 1, 2, 5, 7, 12, 14, 19, 21, 28, 29, 30, 33, and 42 for safety assessments, study drug dosing, sample collections, and other study procedures.

Subjects also will return to the clinic on Day 56 (28 days after receiving their last dose of study drug) for an End-of-Study/Follow-Up visit.

See Table 1 for a schedule of all study events. To assess safety and tolerability, subjects will undergo physical examinations (PEs; including weight), vital sign measurements, clinical (safety) laboratory tests, adverse event (AE) assessments, concomitant medication assessments, and electrocardiograms (ECG).

Number of subjects

Approximately 16; two cohorts of 8 subjects each. An additional cohort of up to 8 subjects may be enrolled. Subjects who withdraw for any reason other than an AE and who do not receive study drug or have only received one dose of study drug may be replaced, up to one subject per cohort. The maximum number of subjects who may be enrolled in this study is 27 (24 + up to 3 replacements, as necessary). Within each dosing cohort, no more than 3 subjects with pemphigus foliaceus may be enrolled.

Diagnosis and main entry criteria

Inclusion criteria:

Subjects must meet the following criteria to be included:

- 1. Willing and able to read, understand and sign an informed consent form;
- 2. Male or female \geq 18 years of age at the time of screening;
- 3. Documented diagnosis of pemphigus vulgaris or foliaceus based on all 3 of the following criteria:
 - a. Documented clinical history consistent with pemphigus vulgaris or foliaceus (clinical presentation defined as mucosal and/ or skin lesions);
 - b. Presence of Anti-Dsg 1 or 3 antibodies above the upper limit of normal:
 - c. History of at least one positive tissue-based test (e.g., biopsy, direct immunofluorescence [DIF])
- 4. Active disease: Lesions lasting > 2 weeks, and 3 active lesions in skin or mucosa or 2 active lesions with at least one being a skin lesion > 1 cm diameter:
 - a. If treated with rituximab or other anti-CD20 antibodies, last dose
 12 months prior to screening;

- b. If being treated with other immunosuppressants (i.e., azathioprine, mycophenolate mofetil or cyclosporine), must be on stable dose (< 10% change in dose) for 6 weeks prior to screening;
- c. If being treated with corticosteroids, must be $\leq 1 \text{mg/kg/day}$ and stable (< 10% change in dose) for 2 weeks prior to screening;
- d. Allowed topical therapies for pemphigus lesions upon entering the study include petroleum jelly or Aquaphor® for the skin or chlorhexidine for the mouth
- 5. Body mass index (BMI) $18.5 35.0 \text{ kg/m}^2$;
- 6. Has a negative urine pregnancy test (for women of childbearing potential) documented prior to the first dose of study drug;
- 7. Females of childbearing potential must agree to be abstinent or else use any two of the following medically acceptable forms of contraception (<1% per year failure rate) from the Screening Period through 60 days after the final study dose: oral contraceptive, condom with or without spermicidal jelly, diaphragm or cervical cap with spermicidal jelly, or intra-uterine device (IUD). A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception.
- 8. Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months do not require contraception during the study.
- 9. Males with female partners of childbearing potential, including males who are surgically sterile (post vasectomy), must agree to be abstinent or else use a medically acceptable form of contraception from the screening period through 60 days after the final study dose.

Exclusion criteria:

Subjects meeting any of the following criteria are to be excluded:

- 1. Subject unable or unwilling to comply with the protocol;
- Active non-hematologic malignancy or history of non-hematologic malignancy in the 3 years prior to screening (exclusive of non-melanoma skin cancer and cervical cancer in situ);
- 3. Positive for HIV or hepatitis C antibody;
- 4. Positive for hepatitis B surface antigen;
- 5. Active infection or history of recurrent infections;
- 6. IVIG use within 60 days of screening;
- 7. Received any cytotoxic (other than azathioprine) or mAb therapy in the 3 months prior to screening;
- 8. Any exposure to an investigational drug or device within the 30 days prior to screening
- 9. Plasmapheresis or immunoadsorption within 60 days of screening

	10. Cellular therapy at any time prior to screening
	11. Use of any immunosuppressive drugs apart from corticosteroids,
	azathioprine, mycophenolate mofetil, or cyclosporine within 3 months of
	screening
	12. Serum total IgG < 600 mg/dL;
	13. Subject has any current medical condition that, in the opinion of the
	Investigator, may compromise their safety or compliance, preclude
	successful conduct of the study, or interfere with interpretation of the results
	(e.g., a significant pre-existing illness or other major comorbidity that the
	Investigator considers may confound the interpretation of the study results);
	14. Any vaccination within 2 weeks of screening
Study drug, dosage,	SYNT001
and administration	Doses: 10 mg/kg and 30 mg/kg. A third cohort of up to 8 subjects may be treated
	at another dose, with a maximum dose of 45 mg/kg, but may also be lower than
	10 mg/kg or between 10 and 30 mg/kg, inclusive.
	SYNT001 is provided as a liquid at a nominal concentration of 50 mg/mL.
	SYNT001 is diluted in Dextrose 5% in Water (D5W) to prepare the solution for
	infusion.
	Route of administration: IV in 250 mL over 1 hour
Control, dose, and	Not applicable
route of	
administration	
Duration of subject	Up to 70 days (10 weeks): Screening of up to 2 weeks (14 days); dosing period
participation and	of 4 weeks (28 days); and 4 weeks (28 days) of follow-up
duration of study	

Prohibited

Concomitant

treatments

All treatments a subject receives within 14 days prior to enrollment through the end of the study (Day 56) will be documented. Concomitant medication and treatment for co-existing conditions, including those for pemphigus, are permitted if not excluded below. Topical antibiotics are permitted to treat active infections that occur on study. Topical or systemic treatments for oral candidiasis are permitted. Topical lidocaine for transient pain relief is acceptable as needed. Significant increases in anti-pemphigus medications may result in subjects being discontinued from the study. Concomitant treatment that is medically indicated for any AEs the subject experiences during the study are permitted.

Use of the following medications will not be permitted during the study unless otherwise specified:

- Rituximab or other anti-CD20 antibody
- Monoclonal antibodies other than study drug
- Any immunosuppressive drugs apart from corticosteroids, azathioprine, mycophenolate mofetil, or cyclosporine
- Topical steroids
- Any dietary herbal supplements
- Any investigational drug or device
- Any vaccinations

If over a period of at least two weeks on study drug, a subject on corticosteroids shows the absence of new lesions and significant healing of lesions that existed at study baseline, a slow corticosteroid taper may be started as per the following suggested schedule

- If on > 30 mg of prednisone per day, decrease by 10 mg every two weeks until a dose of 30 mg per day then decrease by 5 mg every two weeks
- If on < 30 mg of prednisone per day, decrease by 5 mg every two weeks

Safety assessments

Safety assessments include AEs, serious adverse events (SAEs), PEs, vital sign measurements, clinical safety laboratory evaluations, ECGs, and reasons for treatment discontinuations due to toxicity. Safety assessments will be performed at specified time points and prior to discharge from the clinic. Vital sign measurements, including blood pressure, pulse rate, respiratory rate, and temperature will be monitored throughout the study. Pulse oximetry will be monitored during the study drug infusion and for 2 hours following the end of the infusion.

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; Version 4.03) will be used for grading clinical and laboratory AEs.

	The AE reporting period for a subject enrolled in the study begins when the subject provides informed consent and is continued for 28 days after the last dose of study drug. All AEs that occur in the enrolled subjects during the AE reporting period must be recorded, regardless of the relationship of the AE to study drug. Any known untoward event that occurs beyond the AE reporting period that the Investigator assesses as related to study drug should also be recorded.
Dose-escalation rules	Dose-limiting toxicity (DLT) will be defined generally as clinically significant, severe (Grade 3) AEs occurring in ≥ 2 subjects that are determined to be clinically significant and considered related to study drug. If 2 or more subjects at any time in any cohort (8 total subjects per cohort) have
	Grade 3 AEs that are determined to be clinically significant and considered to be related to study drug, dosing will be halted within that cohort and no further dose-escalation will occur. If the dose-escalation stopping rule is met in Cohort 1 (10 mg/kg) all safety data and all available pharmacodynamics data will be reviewed and a cohort may be added at a dose at least 50% lower than the 10 mg/kg dose. If the stopping rule is not met after Cohort 1 (10 mg/kg), dose-escalation may proceed up to a maximum of 30 mg/kg. If the dose-escalation stopping rule is met in Cohort 2, all safety data and all available pharmacodynamics data will be reviewed and a cohort may be added at a dose at least 30% lower than the Cohort 2 dose. If the stopping rule is not met after Cohort 2, dose-escalation may proceed up to a maximum of 45 mg/kg; however, this cohort may also receive a dose equal to or less than 30 mg/kg based on evaluation of all safety and pharmacodynamic data.
Study stopping rule	If any subject experiences a life-threatening AE (Grade 4) that is considered to be related to study drug, any further dosing in all enrolled subjects will be suspended until the DEC has evaluated the event and determined the next appropriate course of action. At any time during the study, the study may be discontinued if the DEC determines that further drug exposure would pose an undue risk to subjects.
Individual stopping rule	Dosing for any individual subject will be discontinued (i.e., further treatment with the study drug will not be given) if the subject experiences any study drug-related SAE or any study drug-related non-SAE adverse event that, in the judgement of the Investigator and Medical Monitor, suggest that it could be unsafe to administer further study drug to that subject. Additionally, a subject may be discontinued from further treatment with study drug, at the discretion of the Investigator with consultation with the Medical Monitor, if they require a

	significant increase in dose(s) of anti-pemphigus medication(s) for the management of pemphigus.				
Pharmacokinetics	The PK of SYNT001 will be evaluated following the first and last (fifth) doses of SYNT001. Starting on Days 0 and 28, serum samples will be collected just prior to the start of study drug infusion (pre-dose), at 5 minutes and 2, 4, 6, 24, and 48 hours after the end-of-study drug infusion. Additional samples will be collected on Days 5 and 33. Study drug concentration will be used to calculate the following PK parameters: $t_{1/2}$, C_{max} , T_{max} , AUC_{0-24} , and $AUC_{0-\infty}$.				
Pharmacodynamics/ Activity	PD samples will be collected for analysis of IgG (serial assessment of IgG levels to identify C _{min} , T _{min}); IgG1-4 subtype levels; IgA levels; IgM levels; albumin levels; anti-Dsg (1 and 3) antibody levels; serum AECA by direct immunofluorescence; CIC; C3; exploratory biomarkers (<i>FCGR2A</i> SNP, RNAseq, urine IgG, CD3 ⁺ CD4 ⁺ T, CD3 ⁺ CD8 ⁺ T, monocytes, NK cells and B cells).				
Immunogenicity	Up to 4 samples will be collected for immunogenicity analyses. Samples will be collected on Days 0 (pre-dose), 14, 28, and 56.				
Skin biopsy	Optional skin biopsy samples will be collected on Day 0 pre-dose and on Days 1, 2, 14, 33 and 56 to analyze SYNT001 levels.				
Photography	Photographs of active lesions will be taken at Day 0. Follow-up photographs of the same areas will be taken on Days 33 and 56. Subjects who begin a steroid taper will have additional photographs taken at the clinic visit during which the decision to begin the taper is made.				
Statistical methods	Sample size consideration				
	Formal sample size calculations were not performed. The number of subjects was chosen based on feasibility and was considered sufficient to meet the study objectives.				
	Data presentations/Descriptive statistics				
	Three populations will be employed in the analysis of study data.				
	The intent-to-treat (ITT) population will consist of all subjects who have received at least one dose of study drug. All safety analyses will be performed on the ITT population.				
	The PK population will consist of all subjects who receive at least one dose of study drug and have sufficient post-dose blood samples to obtain PK parameters.				

• The PD population will consist of all subjects who receive at least one dose of study drug and have post-dose PD data available.

Primary safety analyses will be performed on the ITT population. Demographics, subject disposition, and screening and baseline characteristics will be summarized for the PK and ITT populations, where appropriate.

Criteria for evaluation

Objective	Endpoint							
Primary								
Safety and tolerability of 5 once- weekly IV infusions of SYNT001 to subjects with pemphigus vulgaris or foliaceus	AEs and clinical (safety) laboratory tests							
Secondary								
PK of SYNT001 following a 1-hour IV infusion	$\begin{array}{ c c c c c } \hline PK \ parameters: t_{1/2}, C_{max}, T_{max}, \\ AUC_{0\text{-}24}, and \ AUC_{0\text{-}\infty}. \\ \hline \end{array}$							
Effect of 5 once-weekly IV doses of SYNT001 on: • Total IgG (IgG1-4), IgA, IgM, and albumin • Serum anti-Dsg (1 and 3) antibodies	Changes in levels of IgG, IgG subtypes (IgG1-4), IgA, IgM, albumin, serum anti-Dsg (1 and 3) antibodies							
Assess immunogenicity	Anti-SYNT001 antibodies							
Disease Activity	PDAI Scores							
Exploratory								
Effect of 5 once-weekly IV doses of SYNT001 on biomarkers including: • CIC • C3 • Serum anti-epithelial cell antibody (AECA) levels • Exploratory biomarkers (FCGR2A SNP, RNAseq, urine IgG) • Immune phenotyping by flow cytometry	Changes in CIC; C3; AECA levels by indirect immunofluorescence; <i>FCGR2A</i> SNP; RNAseq; urine IgG, CD3+CD4+ T, CD3+CD8+ T, monocytes, NK cells and B cells; urine IgG levels; changes in blood transcriptome							
Concomitant Treatment	Corticosteroid use during the study							
SYNT001 levels in skin biopsies	Measures of SYNT001 levels in skin biopsies							

Treatment-emergent AEs (TEAEs) will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA®; Version 19 or higher) System Organ Class (SOC) and preferred term, classified from verbatim terms. The incidence and percentage of subjects with at least 1 occurrence of a preferred

term will be included, using the most severe grade. The number of events per preferred term will also be summarized. Causality (relationship to study treatment) will be summarized separately.

TEAEs, SAEs, and AEs leading to withdrawal, or treatment discontinuation will be listed by subject, and cohort using SOC and preferred terms. Duration of AEs will be determined and included in listings, along with action taken, and outcome.

Laboratory results will be summarized by time point and cohort. The incidence of laboratory abnormalities will be summarized. The worst on-study grade after the first dose of study drug will be summarized. Results for variables that are not coded will be presented in the listings as below, within, and above the normal limits of the central laboratory. Vital sign measurements will be summarized by cohort at each scheduled time point using descriptive statistics.

Study drug concentrations will be used to calculate the following PK parameters: $t_{1/2},\,C_{max},\,T_{max},\,$ and area under the curve (AUC). PK parameters will be determined using non-compartmental method(s). Descriptive statistics of PK parameters for SYNT001 will include mean, standard deviation (SD), coefficient of variation (CV), median, minimum, and maximum. T_{max} will be reported as median and range. All descriptive statistics will be performed on untransformed PK parameters and after log_{10} transformation of PK parameters.

PD results will be summarized by cohort. Descriptive statistics of PD parameters for SYNT001 will include mean, SD, CV, median, minimum, and maximum.

Immunogenicity results will be summarized by cohort. Descriptive statistics will include mean, SD, CV, median, minimum, and maximum.

Table 1: Study Assessments

Timepoint (Study Day)	Screen -14 to -1	0	1 (±1 hr)	2 (± 2 hr)	5 ^p (±4 hr)	7 (±4 hr)	12 ^p (±6 hr)	14 (±6 hr)	19 ^p (±6 hr)	21 (±6 hr)	28 (±6 hr)	29 (±1 hr)	30 (±2 hr)	33 (±4 hr)	42 (±3 day)	Follow-Up 56 (±5 days) or ET Visit	Extended Follow- up ^q
Informed Consent	X																
Demographics/Medical History	X																
Inclusion/Exclusion	X																
Physical Examination ^a	X	X				X		X		X	X				X	X	
Vital Signs ^b	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pulse Oximetry ^c		X				X		X		X	X						
Clinical Safety Labs ^d	X	X				X		X		X	X			X	X	X	
Pregnancy test ^e	X	X														X	
Hepatitis & HIV Screen	X																
12-Lead ECG ^f	X	X					X				X					X	
Tetanus & VZV antibodies ^g		X														X	X
PDAI Score		X				X		X		X	X			X	X	X	
PK Sampling ^h		X	X	X	X						X	X	X	X			
Immunogenicity ⁱ		X						X			X					X	
Study Drug Administration ^j		X				X		X		X	X						
Immunoglobulins (IgG, IgA, IgM) and IgG subtypes (IgG 1-4) ^k	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CIC		X			X	X	X	X	X	X	X			X	X	X	
Anti-Dsg (1 & 3) antibody titer	X	X				X		X						X		X	
C3 and AECA ¹		X						X						X		X	
FCGR2A ^m		X															
RNAseq ^m		X						X						X		X	
Urine IgG ^m		X						X						X		X	
Immune phenotyping ⁿ		X									X						
Optional Skin Biopsy		X	X	X				X						X		X	
Photography ^o		X												X		X	
Adverse Events		To be collected from the date that the ICF is signed until 28 days after last dose of study drug.															
Concomitant Medications	To be collected from within 14 days prior to Day 0 through 28 days after last dose of study drug.																

Concomitant Medications

To be collected from within 14 days prior to Day 0 through 28 days after last dose of study drug.

ECG = electrocardiogram; ET= Early Termination; HIV = human immunodeficiency virus; ICF = informed consent form; PD = pharmacodynamic; PK = pharmacokinetic; VZV = varicella-zoster virus

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- a: Complete PE, including weight, to be performed. Height and BMI will be additional assessments conducted at screening.
- b: **Vital sign** measurements (sitting blood pressure, heart rate, respiratory rate, and oral temperature) to be obtained after 5 minutes of seated rest. Any abnormal measurements are to be repeated after 5 minutes of rest. On Days 0, 7, 14, 21, and 28 vital sign measurements will be collected immediately prior to the infusion; 15, 30, and 45 minutes after the start of the infusion; at completion of the infusion; and 30 minutes, 1 hour and 2 hours following completion of the infusion.
- c: **Pulse oximetry:** On Days 0, 7, 14, 21, and 28, pulse oximetry to be measured immediately prior to the infusion; 15, 30, and 45 minutes after the start of the infusion; at completion of the infusion; and 30 minutes, 1 hour and 2 hours following completion of the infusion.
- d: Clinical safety labs: hematology, clinical chemistry, and urinalysis (see Section 6.7 for a complete list). Full clinical safety lab draws will be collected at Screening and on Days 0, 7, 14, 21, 28, 33, 42 and 56.
- e: **Pregnancy test:** To be performed at time of screening and prior to first dose of SYNT001 on Day 0 and on Day 56 (urine or serum test is acceptable, however, positive urine tests must be confirmed with serum testing.)
- f: Digital 12-lead ECG to be obtained after 5 minutes of rest in the supine position and in triplicate at least 1-2 minutes apart (see Section 6.6 for additional information). On Days 0 and 28 to be obtained 5 minutes after the completion of infusion. Day 12 ECG will be collected only if the visit is conducted at the study site.
- g: **Serology**: Testing at Day 56 will not be done for any subject whose baseline titer is below the level of detection. If the Day 56 results are greater than 30% below the baseline value, or if the subject falls below the level of detection, the subject will be re-tested at 1 month after the Follow-Up visit (approximately 2 months after the subject's last dose); if still below the baseline value (or level of detection), the subject will be re-tested after another month (3 months after last dose). Any subject whose baseline value for tetanus or VZV was above the detectable level at baseline, and is not within 30% of the baseline value or is below the detectable level on Day 56 and upon 2 retests (2 and 3 months following last dose of SYNT001), will be referred to their primary care physician for further management. See Section 6.7.3 for additional information.
- h: **PK:** Starting on Days 0 and 28, serum samples will be collected just prior to the start of study drug infusion (pre-dose), and at 5 minutes and 2, 4, 6, 24, and 48 hours after the end-of-study drug infusion. Additional samples will be collected on Days 5 and 33. See Section 6.7.4 for additional information.
- i: Immunogenicity: Blood samples will be collected pre-dose when collected on dosing days. See Section 6.7.6 for additional information.
- j: Prior to **study drug infusion**, SYNT001 drug product is to be diluted in Dextrose 5% in Water (D5W) to a total volume of 250 mL and administered intravenously over 1 hour using a 0.2-micron, inline filter. See Section 9 for additional information.
- k: Immunoglobulins (IgG, IgA, IgM) and IgG subtypes (IgG 1-4): Collected for measurements of IgG, IgG subtypes (IgG1-4), IgA, and IgM at every visit. On Days 0, 7, 14, 21, and 28, samples are collected prior to infusion of study drug. See Section 6.7.5 for additional information
- 1: Exploratory PD samples (C3 and AECA): collected pre-dose when collected on dosing days. See Section 6.7.5 for complete information.
- m: Samples to be collected and stored; pending review of clinical and pharmacodynamics assessments
- n: Immune phenotyping by flow cytometry for measurement of CD3⁺CD4⁺ T, CD3⁺CD8⁺ T, monocytes, NK cells and B cells
- o: Photographs of active lesions taken prior to first dose on Day 0. Follow-up photographs will be taken at Days 33 and 56. Subjects who begin a steroid taper will have additional photographs taken at the clinic visit during which the decision to begin the taper is made.
- p: Visit Days 5, 12 and 19 may be conducted via at-home nursing in lieu of a subject visit to the study site.
- q: Extended follow-up visits will occur only if additional testing for anti-tetanus and/ or anti-VZV titers are required. These visits will occur as needed at approximately 2 months post last dose and 3 months post last dose.

Table 2: Timing Window Allowances for PK/PD Sampling, ECG, and Vital Sign Measurements

Pharmacokinetic and Pharmacodynamic Sampling	
Timepoint	Tolerance Window
0 hour	−240 min to 0 hour
5 minutes post end-of-infusion	± 5 minutes
2, 4, & 6 hours post end-of-infusion	± 15 minutes
24 hours post end-of-infusion	\pm 60 minutes
48 hours post end-of-infusion	± 120 minutes
ECG	
Timepoint	Tolerance Window
5 minutes post end-of-infusion	± 10 minutes
Vital Signs ^a	
Timepoint	Tolerance Window
0 hour	−240 min to 0 hour
15, 30, and 45 minutes after start of infusion	± 5 minutes
60 minutes after start of infusion	± 10 minutes
30, 60 and 120 minutes post end-of-infusion	± 10 minutes

a: Vital signs to include blood pressure, pulse rate, respiratory rate, oral temperature, and pulse oximetry.

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LIST OF ABBREVIATIONS

ADA Anti-drug antibodies

AE Adverse event

AECA Anti-epithelial cell antibody
ALT Alanine aminotransferase
ANA Antinuclear antibody
AST Aspartate aminotransferase
ATC Anatomical therapeutic chemical

AUC₀₋₂₄ Area under the plasma concentration-time curve from pre-dose (time 0) to 24 hours post-dose

 $AUC_{0-\infty}$ Area under the plasma concentration-time curve from pre-dose (time 0) to infinity

BLQ Below the limit of quantification

BMI Body mass index
BUN Blood urea nitrogen

CAR-T Chimeric antigen receptor and T-cell

CFR Code of Federal Regulations
C3 Complement component 3
CBC Complete blood count

CIC Circulating immune complexes

CIDP Chronic inflammatory demyelinating polyneuropathy

C_{max} Maximum plasma concentration determined directly from the concentration-time profile

CRO Contract research organization

CV Coefficient of variation

CVID Common variable immune deficiency

DEC Dose escalation committee
D5W Dextrose 5% in Water
DIF Direct immunofluorescence
DNA Deoxyribonucleic acid
ECG Electrocardiogram

eCRF Electronic case report form
ESR Erythrocyte sedimentation rate
FcGR2a Fc Gamma R2a receptor
FcRn Neonatal Fc receptor

FDA Food and Drug Administration

GCP Good Clinical Practice

GI Gastrointestinal
HBV Hepatitis B virus
HCV Hepatitis C virus

HIPAA Health Insurance Portability and Accountability Act

HIV Human immunodeficiency virus

IB Investigator's brochure IC Immune complex

ICF Informed consent form

ICH International Conference on Harmonization

IgA Immunoglobulin A
IgG Immunoglobulin G
IgG1-4 Immunoglobulin G1-G4
IgM Immunoglobulin M
IL-12 Interleukin 12

IND Investigational new drug
IRB Institutional review board

ITT Intent-to-treat
IUD Intrauterine devices

IV Intravenous

IVIG Intravenous immunoglobulin

MedDRA Medical Dictionary for Regulatory Activities

NHL Non-Hodgkin lymphoma
PD Pharmacodynamics
PE Physical examination
PK Pharmacokinetic
RBC Red blood cells
RNAseq RNA sequencing

QTcF Corrected QT interval using Fridericia's formula

SAE Serious adverse event SAP Statistical analysis plan SAS Statistical Analysis System

SD Standard deviation

SNP Single nucleotide polymorphism

SOC System Organ Class

SOP Standard operating procedures

SYNT001 A humanized, affinity matured IgG4-kappa monoclonal antibody

 $t_{1/2}$ Half-life

TEAE Treatment-emergent adverse event

T_{max} Observed time to reach peak plasma concentration

TNF Tumor necrosis factor ULN Upper limit of normal

UNS Unscheduled

VZV Varicella-zoster virus

WAIHA Warm antibody autoimmune hemolytic anemia

WHO World Health Organization

WHO-DD World Health Organization Drug Dictionary

2 BACKGROUND AND RATIONALE

SYNT001, a humanized, affinity-matured IgG4-kappa monoclonal antibody (mAb), blocks IgG and IgG immune complex (IC) interactions with the neonatal Fc receptor (FcRn) and thereby the major functions of FcRn in protecting IgG and IgG ICs from degradation and their role in downstream signaling events. Specific and high affinity blockade of FcRn with SYNT001 has been shown to increase the catabolism of IgG and IgG IC in healthy volunteers. This predicts that SYNT001 will also accelerate degradation of endogenous circulating IgG autoantibodies and IgG-antigen IC specifically involved in the pathogenesis of autoimmunity. Blocking FcRn interactions with IgG-containing ICs further predicts that SYNT001 will have consequences for innate and adaptive cellular immunity. In the first instance, blocking multimeric IgG IC interactions with FcRn within antigen-presenting cells will result in inhibition of IC-stimulated inflammatory cytokine production and release by these cells. In addition, as FcRn determines the intracellular itinerary of IgG ICs within and among compartments important in cellular immunity, it is anticipated that SYNT001 will block antigen processing and presentation of antigens contained within IC that otherwise lead to CD8⁺ and CD4⁺ T cell activation. Thus, SYNT001 will specifically target immune functions associated with IgG that are involved in certain autoimmune conditions and dismantle their ability to cause disease.

SYNT001 targets key mechanisms contributing to pathology in a variety of IgG-mediated autoimmune disorders, including warm antibody autoimmune hemolytic anemia (WAIHA), pemphigus, and chronic inflammatory demyelinating polyneuropathy (CIDP).

While current treatments for certain autoimmune disorders, including high-dose steroids, immunosuppressants, intravenous immunoglobulin (IVIG), plasmapheresis, and anti-CD20 monoclonal antibodies (mAbs), such as rituximab, can be effective, they are associated with significant adverse effects, as well as delayed or non-durable responses.

Pemphigus is a rare group of blistering autoimmune diseases that affect the skin and mucous membranes. Autoantibodies have been shown to play an important pathogenic role in the mucosal and cutaneous manifestations in patients with pemphigus. Administration of SYNT001, which significantly decreases total IgG, including a corresponding decrease in the level of the pathogenic autoantibodies and the ICs to which they are associated, may lead to a decrease in the mucosal and cutaneous manifestations in patients with pemphigus. Moreover, the ability of SYNT001 to reduce circulating immune complexes (CICs) and the associated innate and adaptive immune responses may allow for further sustained disease modification.

2.1 Study Rationale

This study is being conducted to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity of intravenous (IV) SYNT001 as well as its effects on pemphigus disease activity markers.

2.2 Selection of Doses in this Study

The planned dose levels of SYNT001 for this Phase 1b safety and proof-of-concept study of 10 mg/kg and 30 mg/kg were selected from careful review of the safety, tolerability, and PD effect on total IgG levels after single and repeat dosing of SYNT001 in non-human primates (NHPs), as well as the safety, tolerability, and PD effect on total IgG levels after single ascending doses of SYNT001 in healthy volunteers. In addition, further consideration was given to the desired level of FcRn blockade to achieve suppression of IgG to a range that has been previously correlated with disease remission. Further, we considered the potential effects of inhibiting FcRn function as they relate to immune complex associated innate and adaptive immunity in choosing these dose levels based upon exploratory studies of a single ascending dose of SYNT001 in healthy volunteers. From the NHP studies, single doses of SYNT001 produced a dose-dependent decrease in total IgG and a further decrease was seen with repeated weekly doses up to a maximum 70% reduction at 100 mg/kg. This magnitude of total IgG reduction is approaching the expected maximal effect of 100% inhibition of FcRn function based on murine studies also performed by Syntimmune and others [Roopenian 2003, Nixon 2015]. In the recently completed Phase 1a trial with SYNT001 in healthy volunteers a single dose caused a maximum average 50% drop in total IgG with IV dosing at 30 mg/kg. Based on the NHP studies further reductions are expected following multiple dosing. A comparable decrease in pathogenic autoantibodies is also anticipated.

In the NHP studies, relevant adverse effects, mild-to-moderate infusion reactions, were observed only after the third weekly IV administration, concurrent with the development of anti-SYNT001 antibodies. In the recently completed Phase 1a healthy male volunteer study, the doses of SYNT001 up to and including 30 mg/kg have been well tolerated. There were no dose limiting toxicities, serious adverse events, or any other safety concerns identified. No AEs were observed in the 1 and 3 mg/kg dose cohorts. A single Grade 2 AE was observed; a headache in the 10 mg/kg cohort, treated with acetaminophen. Other subjects had mild (Grade 1) AEs at 10 mg/kg. In Cohort 4 (30 mg/kg), 5 subjects received SYNT001. All five subjects experienced AEs; all were mild (Grade 1), transient and resolved spontaneously without intervention. Therefore, it is anticipated that the doses selected for this study should be well tolerated and have clinically relevant PD effects in patients with chronic pemphigus (vulgaris or foliaceus). For a summary of

findings from the single dose, clinical study in healthy subjects and further details on the nonclinical findings, please refer to the SYNT001 Investigator's Brochure.

2.3 Compliance Statement

This study will be conducted in compliance with Good Clinical Practice (GCP), including the International Conference on Harmonisation (ICH) Guidelines and FDA regulations, consistent with the principles outlined in the Declaration of Helsinki. In addition, the Investigator agrees to adhere to all applicable local laws and regulatory requirements relevant to the use of new therapeutic agents.

The study will be conducted in compliance with the protocol. The appropriate Institutional Review Boards (IRBs) must approve the protocol, any amendments, and the subject informed consent form (ICF) prior to implementation.

Freely given written informed consent must be obtained from every subject prior to participation in this clinical trial. As part of this procedure, the Investigator must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the study subject is aware of the potential risks, inconveniences, or AEs that may occur. The study subject should be informed that he/she is free to withdraw from the study at any time. He/she will receive all information that is required by federal regulations and ICH guidelines. The Investigator or designee will provide the Sponsor with a copy of the IRB-approved informed consent form prior to the start of the study. The rights, safety, and well-being of participating subjects are the most important considerations and should prevail over interests of science and society.

Study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). This trial will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of 5 once-weekly IV infusions of SYNT001 at different dose levels in subjects with chronic pemphigus (vulgaris or foliaceus).

3.2 Secondary Objectives

The secondary objectives of this study are as follow:

- To determine the PK of SYNT001 following 5 once-weekly 1-hour IV infusions at different dose levels
- To assess the effect of 5 once-weekly doses of SYNT001 at different dose levels on the following PD biomarkers:
 - o Immunoglobulins: IgG, IgG subtypes (IgG1-4), IgA, IgM
 - o Albumin
- To assess the effect of 5 once-weekly doses of SYNT001 at different dose levels on the following disease activity markers:
 - o Serum anti-desmoglein (Dsg) (1 and 3) antibody levels
 - o Pemphigus Disease Area Index (PDAI)
- To assess immunogenicity (anti-SYNT001 antibodies)

3.3 Exploratory Objectives

The exploratory objectives of this study are as follow:

- To assess the effect of 5 once-weekly doses of SYNT001 at different dose levels on the following biomarkers, including:
 - o Serum anti-epithelial cell antibody (AECA) levels by indirect immunofluorescence
 - o Circulating immune complexes (CIC)
 - o Complement component 3 (C3)
 - Exploratory biomarkers (FCGR2A single nucleotide polymorphism-SNP, RNAseq, urine IgG)
 - Immune phenotyping by flow cytometry for CD3⁺CD4⁺ T, CD3⁺CD8⁺ T, monocytes, NK cells and B cells
 - o SYNT001 levels in skin biopsies (optional)
- To characterize corticosteroid use during the study

4 STUDY DESIGN

4.1 Study Sites

This study will be conducted at approximately 10 sites in the United States (US).

4.2 Study Endpoints

Primary Outcome Measures: Assessment of safety data (adverse events [AEs], serious adverse events [SAEs], vital sign measurements, ECGs and clinical laboratory tests) will be the primary safety measure.

Secondary Outcome Measures

Pharmacokinetics:

Half-life (t_{1/2}), maximum plasma concentration determined directly from the concentration-time profile (C_{max}), observed time to reach peak plasma concentration (T_{max}), area under the plasma concentration-time curve from pre-dose (time 0) to 24 hours post-dose (AUC₀₋₂₄), and area under the plasma concentration-time curve from pre-dose (time 0) to infinity (AUC_{0-∞})

PD Biomarkers:

- Ig Assessments: Serial assessments of total IgG and IgG subtypes (IgG1-4)
 - o Serial assessments of total IgG and IgG subtypes (IgG1-4)
 - o IgA levels
 - o IgM levels
- Albumin levels

Disease activity markers:

- Serum anti-desmoglein (Dsg) (1 and 3) antibody levels
- Pemphigus Disease Area Index (PDAI) scores

Immunogenicity:

• Anti-SYNT001 antibodies

Exploratory Outcome Measures

Biomarkers, including:

- CIC
- C3
- Serum AECA levels
- Exploratory biomarkers (FCGR2A SNP, RNAseq, urine IgG)

- Immune phenotyping by flow cytometry for measurement of CD3⁺CD4⁺ T, CD3⁺CD8⁺ T, monocytes, NK cells and B cells
- SYNT001 levels in skin biopsies (optional)

Concomitant Treatments

Corticosteroid use

Further details on the statistical and analytical plan for these endpoints are available in Section 12, Statistical Considerations.

4.3 Overview of Study Design

This will be a multicenter, open-label study to assess the safety, tolerability, activity, PK, PD, and immunogenicity of 5 once-weekly IV infusions of SYNT001 to subjects with chronic pemphigus (vulgaris or foliaceus).

Planned doses of SYNT001 to be studied are 10 mg/kg and up to 30 mg/kg. Two cohorts of 8 eligible subjects each will receive 5 once-weekly 60-minute infusions of SYNT001 10 mg/kg or up to 30 mg/kg. Based on review of safety, PD, and clinical outcomes of the first cohort, the dose for the second cohort may be adjusted, but with a maximum dose of 30 mg/kg. Based on review of safety, PD and clinical outcomes from these 2 cohorts, a third cohort of up to 8 subjects may be treated at another dose, with a maximum dose of 45 mg/kg, but may also be lower than 10 mg/kg or between 10 and 30 mg/kg, inclusive.

Cohort	No. of Subjects	Dose
1	8	SYNT001 10 mg/kg
2	8	SYNT001 30 mg/kg

Cohorts will be dosed sequentially beginning with Cohort 1. The first 2 subjects will be dosed at least 24 hours apart. A review of the 24-hour safety data for the first subject will be performed to ensure that there are no overt safety concerns before dosing the second subject. A review of the 7-day safety data for the first 2 subjects will be performed prior to dosing the remaining 6 subjects in the cohort. This evaluation will include a review of AE/SAE reports, vital sign assessments, physical examinations, ECGs and clinical laboratory testing. The seriousness, severity, and relatedness of AEs/SAEs will also be considered in the safety evaluation. Safety data will be reviewed on a continuous basis throughout the study. All data through Day 42

(2 weeks after the last subject's last dose in Cohort 1) will be reviewed before Cohort 2 is initiated. Cohort 2 and Cohort 3, if added, will be dosed per the same schedule.

Safety evaluations will be conducted by a dose escalation committee (DEC). The DEC will consist of the Medical Monitor, an Independent Clinical Expert and a Syntimmune Medical Officer. To assist in the safety assessments, the DEC may request that Investigators, other experts, or members within their organizations review the data and participate in the discussions. Dosing and dose escalation will proceed if the DEC has determined that it would be safe and appropriate to do so. In addition, over the course of the study, the DEC will review any drug-related SAEs to determine if modifications to the study or other measures are necessary to ensure the safety of the subjects.

On days where study drug is administered, vital sign and pulse oximetry measurements will be collected immediately prior to the infusion; 15, 30, and 45 minutes after the start of the infusion; at completion of the infusion; and 30 minutes, 1 hour and 2 hours following completion of the infusion.

On Days 0 and 28, PK blood samples will be collected prior to infusion start and then over the subsequent 48 hours. Subjects will remain at the clinic through the 6-hour PK sample collection and will return to the clinic for the 24- and 48-hour collections. Additional samples will be collected on Days 5 and 33.

On Day 0 photographs will be taken of active lesions. Follow-up photographs will be taken of the same areas on Days 33 and 56. If a subject begins a steroid taper, additional photographs will be taken at the clinic visit during which the decision to begin the taper is made.

Subsequent visits will occur on Days 1, 2, 5, 7, 12, 14, 19, 21, 28, 29, 30, 33, and 42 for safety assessments, study drug dosing, sample collections, and other study procedures.

Subjects also will return to the clinic on Day 56 (28 days after receiving their last dose of study drug) for an End-of-Study/Follow-Up visit.

See Table 1 for a schedule of all study events. To assess safety and tolerability, subjects will undergo physical examinations (PEs; including weight), vital sign measurements, clinical (safety) laboratory tests, AE assessments, concomitant medication assessments, and electrocardiograms (ECG).

Note: No vaccinations may be given from within 2 weeks of screening until 2 months following the last dose of study drug.

4.4 Randomization and Blinding

This is an open-label study.

5 STUDY POPULATION

5.1 Target Population

This study will be conducted in approximately 16 male and female subjects (2 cohorts of 8 subjects each) with a confirmed diagnosis of pemphigus (vulgaris or foliaceus); however, a third cohort of up to 8 subjects may be added. Subjects will be enrolled only once in the study and will not be included in subsequent dosing cohorts. Subjects who withdraw for any reason other than an AE and who do not receive study drug or have only received one dose of study drug may be replaced, up to one subject per cohort. Subjects who do not receive all doses of study drug will continue to be followed through 28 days after their last dose. The maximum number of subjects who may be enrolled in this study is 27 (24 + up to 3 replacements, as necessary). Within each dosing cohort, no more than 3 subjects may be enrolled with pemphigus foliaceus.

5.2 Inclusion Criteria

A subject must meet the following criteria to be eligible for the study:

- 1. Willing and able to read, understand and sign an informed consent form;
- 2. Male or female \geq 18 years of age;
- 3. Documented diagnosis of pemphigus vulgaris or foliaceus based on all 3 of the following criteria:
 - a. Documented clinical history consistent with pemphigus vulgaris or foliaceus (clinical presentation defined as mucosal and/ or skin lesions);
 - b. Presence of Anti-Dsg 1 or 3 antibodies above the upper limit of normal;
 - c. History of at least one positive tissue based test (biopsy, DIF)
- 4. Active disease: Lesions lasting > 2 weeks, and 3 active lesions in skin or mucosa or 2 active lesions with at least one being a skin lesion > 1 cm diameter:
 - a. If treated with rituximab or other anti-CD20 antibodies, last dose > 12 months prior to screening;
 - b. If being treated with other immunosuppressants (i.e., azathioprine, mycophenolate mofetil or cyclosporine), must be on stable dose (< 10% change in dose) for 6 weeks prior to screening;
 - c. If being treated with corticosteroids, must be ≤ 1mg/kg/day and stable (< 10% change in dose) for 2 weeks prior to screening;

- d. Allowed topical therapies for pemphigus lesions upon entering the study include petroleum jelly or Aquaphor® for the skin or chlorhexidine for the mouth
- 5. Body mass index (BMI) $18.5 35.0 \text{ kg/m}^2$;
- 6. Has a negative urine pregnancy test (for women of childbearing potential) documented prior to the first dose of study drug;
- 7. Females of childbearing potential must agree to be abstinent or else use any two of the following medically acceptable forms of contraception (<1% per year failure rate) from the Screening Period through 60 days after the final study dose: oral contraceptive, condom with or without spermicidal jelly, diaphragm or cervical cap with spermicidal jelly, or intra-uterine device (IUD). A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception.
- 8. Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months do not require contraception during the study.
- 9. Males with female partners of childbearing potential, including males who are surgically sterile (post vasectomy), must agree to be abstinent or else use a medically acceptable form of contraception from the screening period through 60 days after the final study dose.

5.3 Exclusion Criteria

A subject who meets any of the following criteria is ineligible for the study:

- 1. Unable or unwilling to comply with the protocol;
- Active non-hematologic malignancy or history of non-hematologic malignancy in the 3 years prior to screening (exclusive of non-melanoma skin cancer and cervical cancer in situ);
- 3. Positive for HIV or hepatitis C antibody;
- 4. Positive for hepatitis B surface antigen;
- 5. Active infection or history of recurrent infections;
- 6. IVIG treatment within 60 days of screening;

- 7. Received any cytotoxic (other than azathioprine) or mAb therapy in the 3 months prior to screening;
- 8. Any exposure to an investigational drug or device within 30 days prior to screening;
- 9. Plasmapheresis or immunoadsorption within 60 days of screening
- 10. Cellular therapy at any time prior to screening
- 11. Use of any immunosuppressive drugs apart from corticosteroids, azathioprine, mycophenolate mofetil, or cyclosporine within 3 months of screening;
- 12. Serum total IgG < 600 mg/dL;
- 13. Subject has any current medical condition that, in the opinion of the Investigator, may compromise their safety or compliance, preclude successful conduct of the study, or interfere with interpretation of the results (e.g., a significant pre-existing illness or other major comorbidity that the Investigator considers may confound the interpretation of the study results);
- 14. Any vaccination within 2 weeks of screening

6 STUDY PROCEDURES

6.1 Informed Consent

All subjects must take part in the informed consent process. Adequate time must be allowed for the subject to ask questions and make a voluntary decision. No protocol-specific procedures, including screening procedures, are to be performed until the subject has signed and dated an IRB-approved ICF. Subjects may withdraw consent at any time. Participation in the study may be terminated at any time without the subject's consent as determined by the Investigator.

6.2 Demographics and Medical History

Demographics (age, gender, race and ethnicity) and medical history will be obtained from the subject and recorded on the source document and eCRF. Medical history will capture the subject's current medical history (current disease processes), past medical status (past disease processes), history of surgery and concomitant treatments.

6.3 Physical Examination

A complete physical examination will be performed as outlined in Table 1. The complete PE will include measurements of weight (in kg) and height (in cm; height to be measured only at screening visit) and a review of the following body systems:

- General appearance
- Head, eyes, ears, nose, and throat
- Neck
- Respiratory
- Cardiovascular
- Abdomen
- Neurologic
- Extremities
- Dermatologic
- Lymphatic

Any abnormal and clinically significant findings from the PE must be recorded in the appropriate eCRF. Findings at screening and Day 0 (pre-dose) will be recorded as medical history.

6.4 Pemphigus Disease Area Index (PDAI) Scoring

Pemphigus severity and disease activity will be measured using the PDAI. See Appendix B.

6.5 Vital Sign Measurements

Vital sign measurements will be collected after the subject has been sitting for 5 minutes. Vital sign assessments will include measurements of sitting blood pressure (mm Hg), heart rate (beats

per minute), respiration rate (breaths per minute), oral temperature (Celsius). Abnormal results are to be repeated after 5 minutes of rest. Pulse oximetry (%) also is to be measured. See Table 2 for timing window allowances with respect to measurement collection.

On Days 0, 7, 14, 21, and 28, vital sign measurements are to be obtained immediately prior to the infusion; 15, 30, and 45 minutes after the start of the infusion; at completion of the infusion; and 30 minutes, 1 hour and 2 hours following completion of the infusion. Details on the management of mild to moderate and severe infusion reactions can be found in Figure 1 and Figure 2. Abnormalities in vital sign measurements will be graded in severity per the NCI CTCAE scale Version 4.03.

Subjects should be seated quietly for at least 5 minutes in a chair with their backs supported, their feet flat on floor (legs uncrossed), and their arms bared on a hard surface, with the arm slightly abducted and bent, with palm up and the midpoint of upper arm at heart level. Correct cuff and bladder size should be utilized and the same cuff and arm should be used per subject throughout study.

6.6 12-Lead Electrocardiogram (ECG)

Digital 12-lead ECG measurements will be obtained at screening, on Days 0 and 28 at 5 minutes after the completion of the infusion and at the Day 56 (Follow-Up) Visit. Subjects who conduct their Day 12 visit at the investigative site, as opposed to an at-home nurse visit, will have an additional ECG performed. ECGs are to be performed with the subject in a supine position having rested in this position for at least 5 minutes before each reading. ECGs are to be performed in triplicate, each 1 to 2 minutes apart. See Table 2 for timing window allowances with respect to performing ECG.

The following ECG parameters will be collected: PR interval, RR interval, QRS interval, and QT interval. The ECG findings will be evaluated by a qualified physician for the presence of abnormalities (qualitative assessment). The physician will assess each ECG as normal, abnormal/not clinically significant, or abnormal/clinically significant.

Normal QTcF is ≤ 450 msec.

Abnormalities in the ECG that appear following therapy or that result in clinical signs and symptoms are considered clinically significant for the purposes of this study and will be recorded on the AE eCRF.

6.7 Clinical Laboratory Measurements

Collection time for all safety, PD, and exploratory labs are outlined in Table 1.

Laboratory testing (hematology, urinalysis, serum chemistry, virology, serology, pregnancy tests, PD samples, PK samples, and anti-drug antibody samples) will be performed using established methods by a central laboratory. Safety laboratory panels are defined as listed in Table 3. Blood and urine samples for hematology, serum chemistry, and urinalysis will be prepared using standard procedures. Results will be provided to the Investigator. Aliquots from the PK, biomarker and anti-drug antibody samples may be retained as back-up for additional testing as necessary. Subjects will be in a seated or supine position during blood collection. Full clinical safety lab draws will be collected at Screening and on Days 0, 7, 14, 21, 28, 33, 42 and 56. The total blood draw for each subject who completes the study at Day 56, will be approximately 311 mL. Please refer to the Laboratory Manual for more information.

Table 3: Clinical Laboratory Panels

Hematology	Serum Chemistry	Urinalysis	
CBC with differential Erythrocyte Sedimentation Rate (ESR)	 Albumin Alkaline phosphatase ALT AST BUN Calcium Carbon dioxide Chloride Creatinine Glucose LDH Phosphorus Potassium Sodium Total and direct bilirubin Total protein Uric acid C-Reactive Protein 	 Appearance Color pH Specific gravity Ketones Protein Glucose Nitrite Urobilinogen Blood/hemoglobin Leukocyte esterase Bilirubin Microscopic examination of sediment: only if the results of the urinalysis dipstick evaluation are positive for blood/hemoglobin 	
Virology			
Hepatitis CHepatitis B			

- HIV
- VZV
- Tetanus

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count; BUN = blood urea nitrogen; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; VZV = varicella-zoster virus

Abnormalities in clinical laboratory tests that are considered clinically significant are to be recorded on the AE electronic case report form (eCRF) page. Laboratory results will be graded using the NCI CTCAE, Version 4.03. If laboratory values constitute part of an event that meets criteria defining it as serious, the event (and associated laboratory values) must be reported as an SAE (see Section 11.3.1).

6.7.1 Pregnancy Testing

Pregnancy testing will be performed for women of childbearing potential at screening and prior to first dose of SYNT001 on Day 0 and Day 56 (urine or serum test is acceptable however, positive urine tests must be confirmed with serum testing.)

6.7.2 Virology

Testing for HCV antibody, hepatitis B surface antigen, and HIV antibody will be performed at screening.

6.7.3 Serum Tetanus Antibody and Varicella-Zoster Virus Antibody Testing

Samples for serum tetanus antibody and varicella-zoster virus antibody testing are to be collected at baseline (pre-dose, Day 0) and on Day 56 (Follow-Up visit). Testing at Day 56 will not be done for any subject whose baseline titer is below the level of detection. Specifically, if the baseline VZV titer is above the detectable level, but tetanus is not, only the VZV antibody titer will be tested on Day 56. If the Day 56 results are below the baseline value, defined as greater than 30% below the baseline value, or if the subject falls below the level of detection, the subject will be re-tested at 1 month after the Follow-Up visit (approximately 2 months after the subject's last dose); if still below the baseline value (or level of detection), the subject will be re-tested after another month (3 months after last dose). Any subject whose baseline value for tetanus or VZV was above the detectable level at baseline, and is not within 30% of the baseline value or is below the detectable level on Day 56 and upon 2 retests (2 and 3 months following last dose of SYNT001), will be referred to their primary care physician for further management.

6.7.4 Pharmacokinetics (PK) Sampling

Starting on Days 0 and 28, serum samples will be collected just prior to the start of study drug infusion (pre-dose), at 5 minutes and 2, 4, 6, 24, and 48 hours after the end-of-study drug infusion. Additional samples will be collected on Days 5 and 33. The actual time and date of each blood draw is to be recorded.

Study drug concentration will be used to calculate the following PK parameters: $t_{1/2}$, C_{max} , T_{max} , AUC_{0-24} , and $AUC_{0-\infty}$.

Detailed instructions for sample collection and preparation will be provided in a separate laboratory manual

6.7.5 Pharmacodynamic Sampling

PD samples will be collected for analyses throughout the study. On Days 0, 7, 14, 21, and 28, samples should be collected prior to infusion of study drug. Measurements for albumin PD biomarkers will be derived from the clinical safety laboratory results. Samples for each type of PD will be collected according to the schedule shown in Table 4.

Table 4: Pharmacodynamic/ Activity Assessments

Parameter	Collection Timepoints	
IgG, IgG subtypes (IgG1-4), IgA, IgM	Screening, and Days 0, 1, 2, 5, 7, 12, 14, 19, 21, 28, 29, 30, 33, 42, and 56	
Circulating immune complexes (CIC)	Days 0, 5, 7, 12, 14, 19, 21, 28, 33, 42, and 56	
Albumin	Screening, and Days 0, 7, 14,21, 28, 33, 42, and 56	
Anti-Dsg (1 and 3) antibody titer	Screening, Days 0, 7, 14, 33, and 56	
 Complement component 3 (C3) Anti-epithelial cell antibody (AECA) levels by indirect immunofluorescence 	Days 0, 14, 33, and 56	
Exploratory biomarker (RNAseq, Urine IgG)	Days 0, 14, 33, and 56	
Immune phenotyping by flow cytometry for measurement of CD3 ⁺ CD4 ⁺ T, CD3 ⁺ CD8 ⁺ T, monocytes, NK cells and B cells	Days 0 and 28	
Exploratory biomarker (FCGR2A SNP)	Day 0	

See Table 2 for timing window allowances with respect to measurement collection. Detailed instructions for sample collection (including collection tubes) and preparation will be provided in a separate laboratory manual.

6.7.6 Immunogenicity Testing

Up to 4 serum samples will be collected for immunogenicity analyses. Samples will be collected on Days 0 (pre-dose), 14, 28, and 56.

SYNT001 is being developed for the acute and chronic therapy of autoimmune disorders. Although SYNT001 is a humanized IgG4 monoclonal antibody, exposure to SYNT001 in clinical trials could result in the development of anti-drug antibodies (ADAs), with potential consequences ranging from neutralization or lessening of drug efficacy to safety consequences such as allergic reactions. Testing will first detect binding ADAs, then, for all confirmed positive samples, there will be testing for neutralizing effects.

Detailed instructions for sample collection and preparation will be provided in a separate laboratory manual.

6.8 Study Drug Administration

Two cohorts of 8 eligible subjects each will receive 5 once-weekly 60-minute IV infusions of SYNT001 10 mg/kg or up to 30 mg/kg. SYNT001 will be given as a 250-mL IV infusion over 1 hour using a 0.2-micron, inline filter. Based on review of safety data, as well as available and relevant PD results, and clinical outcomes of Cohort 1, a decision about proceeding with Cohort 2 will be made. Based on review of all safety data, available PD results, and clinical outcomes of these 2 cohorts, a third cohort of 8 subjects may be treated at another dose, with a maximum dose of 45 mg/kg, but may also be lower than 10 mg/kg or between 10 and 30 mg/kg, inclusive.

Cohort No.	Study Drug	Dose Level (mg/kg/dose)
1	SYNT001	10 mg/kg
2	SYNT001	30 mg/kg

See Section 9.1 for dosing schedule.

6.9 Prior and Concomitant Medications

All medications a subject receives within 14 days prior to enrollment through the end of the study (Day 56) will be documented on the source document and eCRF.

Note: No vaccinations may be given from within 2 weeks of screening until 2 months following the last dose of study drug.

6.10 Adverse Event Assessments

Information regarding the occurrence of AEs will be collected from the time the subject signs the informed consent form throughout their participation in the study, including a period of 28 days after study drug dosing. Findings at screening and Day 0 (pre-dose) will be recorded as medical history. Any known untoward event that occurs beyond the AE reporting period that the Investigator assesses as related to study drug also should be reported as an AE.

Clinical AEs will be graded using the NCI CTCAE, Version 4.03 (Appendix A).

Note: AEs resulting in a subject's permanent discontinuation from the study, regardless of seriousness or relationship to study drug, MUST be promptly reported to the sponsor. Additionally, subjects must be followed until return to normal and/or resolution of the AE.

See Section 11 for more information.

6.11 Photographs

On Day 0 photographs will be taken of active lesions. Follow-up photographs will be taken of the same areas on Days 33 and 56. Subjects who begin a steroid taper will have additional photographs taken at the clinic visit during which the decision to begin the taper is made. A separate manual describing the procedures for taking photographs will be provided.

6.12 Skin Biopsy

Optional skin biopsy samples will be collected on Day 0 pre-dose and on Days 1, 2, 14, 33 and 56 to analyze SYNT001 levels.

7 STUDY ASSESSMENTS

7.1 Screening Period: Day -14 to Day -1

Informed consent must be obtained before any study-specific samples are taken or study-specific tests or evaluations are conducted. The following assessments at the screening visit are to occur within 14 days before dosing. Study eligibility will be based on satisfying all the study inclusion and exclusion criteria.

At the screening visit, information will be collected and subjects will have clinical evaluations as follows:

- Informed consent (Section 6.1)
- Medical history and demographic data (Section 6.2)
- Review inclusion and exclusion criteria (Section 5.2, Section 5.3)
- Complete PE, including height and weight (Section 6.3)
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- 12-Lead ECG (to be obtained in triplicate after 5 minutes of rest in the supine position) (Section 6.6)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- Pregnancy test (Section 6.7)
- Hepatitis and HIV screen (Section 6.7)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - Anti-Dsg (1 and 3) antibody titer
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.2 Enrollment and First Treatment: Day 0

Study Day 0 is defined as the date the subject is administered their first dose of study drug. On Day 0, subjects will be asked to come to the clinic and the following procedures will be performed prior to the first dose of study drug:

- Complete physical exam (Section 6.3)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature); to be measured immediately prior to the infusion (Section 6.5)
- Pulse oximetry (to be measured immediately prior to the infusion) (Section 6.5)

- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- Pregnancy test (Section 6.7)
- Serum tetanus antibody and VZV antibody (Section 6.7)
- PDAI Score (Section 6.4)
- PK baseline sample collection (collected just prior to the start of the study drug infusion) (Section 6.7)
- Immunogenicity sample collection (collected just prior to the start of study drug infusion) (Section 6.7)
- PD sample collection (collected just prior to the start of the study drug infusion) (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - Anti-Dsg (1 and 3) antibody titer
 - CIC
 - C3
 - AECA
 - FCGR2A SNP
 - RNAseq
 - Urine IgG
 - Immune phenotyping
- Optional skin biopsy (Section 6.12)
- Photography (Section 6.11)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After the preceding procedures and assessments are completed:

- Study drug administration (record date and time of dose of study drug) (Section 9)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) will be performed at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion (Section 6.5)
- Pulse oximetry will be measured at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion (Section 6.5)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After administration of study drug, the following post treatment procedures and assessments will be performed:

• Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral

temperature): 30 minutes, 1 hour and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest (Section 6.5)

- Pulse oximetry: 30 minutes, 1 hour and 2 hours following completion of the infusion (Section 6.5)
- PK sample collection at 5 minutes and 2, 4, 6 hours after the end-of-study drug infusion; record collection date and time for each PK sample (Section 6.7)
- 12-Lead ECG (to be obtained in triplicate at 5 minutes after the completion of study drug infusion (Section 6.6)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.3 Follow-up: Day 1

On Day 1 (24 hours \pm 1 hour from end-of-infusion time on Day 0), the subject will return to the clinic and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
- PK sampling (record collection date and time) (Section 6.7)
- Optional skin biopsy (Section 6.12)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.4 Follow-up: Day 2

On Day 2 (48 hours \pm 2 hours from end-of-infusion time on Day 0), the subject will return to the clinic and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
- PK sampling (record collection date and time) (Section 6.7)
- Optional skin biopsy (Section 6.12)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.5 Follow-up: Day 5

On Day 5 (120 hours \pm 4 hours from end-of-infusion time on Day 0), subjects may return to the clinic or be visited by at-home nurse, and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- PK sampling (record collection date and time) (Section 6.7)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.6 Treatment Day 7 (Dose 2)

On Day 7 (\pm 6 hours) subjects will return to the clinic and the following procedures are to be performed prior to study drug infusion:

- Complete physical exam (Section 6.3)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature); to be measured immediately prior to the infusion (Section 6.5)
- Pulse oximetry (to be measured immediately prior to the infusion) (Section 6.5)
- PDAI Score (Section 6.4)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- PD sample collection (collected just prior to the start of the study drug infusion) (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titer
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After the preceding procedures and assessments are completed:

- Study drug administration (record date and time of dose of study drug) (Section 9)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) will be performed at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion (Section 6.5)
- Pulse oximetry will be measured at 15, 30, and 45 minutes after the start of the infusion

and at completion of the infusion (Section 6.5)

- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After administration of study drug, the following post treatment procedures and assessments will be performed:

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature): 30 minutes, 1 hour and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Pulse oximetry: 30 minutes, 1 hour and 2 hours following completion of the infusion (Section 6.5)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.7 Dose 2 Follow-up Day 12

On Day 12 (\pm 6 hours) the subject may will return to the clinic, or be visited by at-home nurse, and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
- If visit performed at the study site: 12-Lead ECG to be obtained in triplicate (Section 6.6)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.8 Treatment Day 14 (Dose 3)

On Day 14 (\pm 6 hours) subjects will return to the clinic and the following procedures are to be performed prior to study drug infusion:

- Complete physical exam (Section 6.3)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature); to be measured immediately prior to the infusion (Section 6.5)
- Pulse oximetry (to be measured immediately prior to the infusion) (Section 6.5)
- PDAI Score (Section 6.4)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)

- Immunogenicity sample collection (collected just prior to the start of study drug infusion) (Section 6.7)
- PD sample collection (collected just prior to the start of the study drug infusion) (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - Anti-Dsg (1 and 3) antibody titer
 - CIC
 - C3
 - AECA
 - RNAseq
 - Urine IgG
- Optional skin biopsy (Section 6.12)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After the preceding procedures and assessments are completed:

- Study drug administration (record date and time of dose of study drug) (Section 9)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) will be performed at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion (Section 6.5)
- Pulse oximetry will be measured at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion (Section 6.5)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After administration of study drug, the following post treatment procedures and assessments will be performed:

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature): 30 minutes, 1 hour and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Pulse oximetry: 30 minutes, 1 hour and 2 hours following completion of the infusion (Section 6.5)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.9 Dose 3 Follow-up Day 19

On Day 19 (\pm 6 hours) the subject may return to the clinic, or be visited by an at-home nurse, and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.10 Treatment Day 21 (Dose 4)

On Day 21, $(\pm 6 \text{ hours})$ subjects will return to the clinic and the following procedures are to be performed prior to study drug infusion:

- Complete physical exam (Section 6.3)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature); to be measured immediately prior to the infusion (Section 6.5)
- Pulse oximetry (to be measured immediately prior to the infusion) (Section 6.5)
- PDAI Score (Section 6.4)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- PD sample collection (collected just prior to the start of the study drug infusion) (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After the preceding procedures and assessments are completed:

- Study drug administration (record date and time of dose of study drug) (Section 9)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) will be performed at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion (Section 6.5)
- Pulse oximetry will be measured at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion (Section 6.5)
- Concomitant medication assessment (Section 6.9)

• AE assessment (Section 6.10)

After administration of study drug, the following post treatment procedures and assessments will be performed:

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature): 30 minutes, 1 hour and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Pulse oximetry: 30 minutes, 1 hour and 2 hours following completion of the infusion (Section 6.5)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.11 Treatment Day 28 (Dose 5)

On Day 28 (\pm 1 Day), subjects will return to the clinic and the following procedures are to be performed prior to study drug infusion:

- Complete physical exam (Section 6.3)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature); to be measured immediately prior to the infusion (Section 6.5)
- Pulse oximetry (to be measured immediately prior to the infusion) (Section 6.5)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- PDAI Score (Section 6.4)
- PK sampling (collected just prior to the start of the study drug infusion; record collection date and time for each PK sample) (Section 6.7)
- Immunogenicity sample collection (collected just prior to the start of study drug infusion) (Section 6.7)
- PD sample collection (collected just prior to the start of the study drug infusion) (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Immune phenotyping
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After the preceding procedures and assessments are completed:

- Study drug administration (record date and time of dose of study drug) (Section 9)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) will be performed at 15, 30, and 45 minutes after the start of the infusion

- and at completion of the infusion (Section 6.5)
- Pulse oximetry will be measured at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion (Section 6.5)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After administration of study drug, the following post treatment procedures and assessments will be performed:

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature): 30 minutes, 1 hour and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Pulse oximetry: 30 minutes, 1 hour and 2 hours following completion of the infusion (Section 6.5)
- PK sample collection at 5 minutes and 2, 4, 6 hours after the end-of-study drug infusion; record collection date and time for each PK sample (Section 6.7)
- 12-Lead ECG (to be obtained in triplicate at 5 minutes after the completion of study drug infusion (Section 6.6)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.12 Follow-up Day 29

On Day 29 (24 hours \pm 1 hour from end-of-infusion time on Day 28), the subject will return to the clinic and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
- PK sampling (record collection date and time) (Section 6.7)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.13 Follow-up Day 30

On Day 30 (48 hours \pm 2 hours from end-of-infusion time on Day 28), the subject will return to the clinic and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
- PK sampling (record collection date and time) (Section 6.7)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.14 Follow-up Day 33

On Day 33 (120 hours \pm 4 hours from end-of-infusion time on Day 28), subjects will return to the clinic and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- PDAI Score (Section 6.4)
- PK sampling (record collection date and time) (Section 6.7)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titer
 - C3
 - AECA
 - RNAseq
 - Urine IgG
- Optional skin biopsy (Section 6.12)
- Photography (Section 6.11)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.15 Follow-up Day 42

On Day 42 (\pm 3 days), subjects will return to the clinic and the following procedures are to be performed:

- Complete physical exam (Section 6.3)
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.16 Follow-up Day 56 (End-of-Study) or Early Termination Visit

On Day 56 (\pm 5 days), subjects are to return to the clinic and the following procedures are to be performed:

- Complete physical exam (Section 6.3)
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- Pregnancy test (Section 6.7)
- 12-Lead ECG (to be obtained in triplicate after 5 minutes of rest in the sitting position) (Section 6.5)
- Serum tetanus antibody and VZV antibody; Testing at Day 56 will not be done for any subject whose baseline titer is below the level of detection. See Section 6.7.3 for additional information.
- Immunogenicity sample collection (Section 6.7)
- PDAI Score (Section 6.4)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titer
 - C3

- AECA
- RNAseq
- Urine IgG
- Optional skin biopsy (Section 6.12)
- Photography (Section 6.11)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.17 Extended Follow-up Visits

Extended follow-up visits will occur only if additional testing for anti-tetanus and/ or anti-VZV titers are required. These visits will occur as needed at approximately 2 months post last dose and 3 months post last dose. See Section 6.7.3.

8 REMOVING SUBJECTS FROM STUDY

Every reasonable effort will be made to keep the subject in the study; however, if a subject is withdrawn from the study, every effort will be made by the Investigator to complete and report the reasons for withdrawal as thoroughly as possible. The reason(s) for termination must be clearly documented on the appropriate page of the eCRF. Once a subject discontinues from the study for any reason, every effort will be made to collect all clinical and laboratory data as scheduled for the Early Termination Visit (See Table 1). A termination eCRF must be completed for all enrolled subjects.

8.1 Subject Withdrawal

A subject's participation in the study may be prematurely discontinued for any of the following reasons:

- 1. The subject wishes to withdraw from the study.
- 2. Request by a regulatory agency (e.g., Institutional Review Board).
- 3. Subject experiences a significant or intolerable AE.
- 4. The subject experiences a significant adverse change in vital signs, PE findings, or a clinical laboratory parameter.
- 5. The subject has a need for a concomitant medication that is not permitted by the study protocol.
- 6. The subject experiences generalized impairment or mental incompetence that would result in the subject being unable to understand his or her participation in the study.
- 7. If, in the Investigator's medical judgment, further participation would be injurious to the health and well-being of the subject, or is not in the best interest of the subject.
- 8. Administrative reasons, such as subject non-compliance or a major protocol violation.

Subjects who are withdrawn from this study due to an AE determined to be related to study drug are to be followed until there is either:

- Resolution or stabilization of the AE determined to be related
- The subject is lost to follow-up
- The event is otherwise explained

If there is a persistent AE contributing to discontinuation that is determined to be related to SYNT001, subjects must be followed with appropriate medical management until resolution or stabilization.

A reasonable effort should be made to contact any subject lost to follow-up during the study to complete assessments and retrieve any outstanding data. If the subjects are unreachable by telephone after three (3) attempts, the minimum of a registered letter should be sent requesting that contact be made with the Investigator to report survival information.

8.2 Study Discontinuation

Syntimmune Inc. has the right to terminate or to stop the study at any time. Reasons for study discontinuation may include, but are not limited to the following:

- The incidence or severity of AEs in this or other related studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory
- Drug supply issues
- Excessive subject self-withdrawal
- Significant protocol violations (e.g., violation of eligibility criteria, dosing errors, missing data for study endpoint analysis)

8.3 Replacements

Enrolled subjects withdrawn for a reason other than an AE will be replaced if they have not been dosed or have only received one dose of study drug at the time of discontinuation, up to one subject per cohort. Subjects who do not receive all doses of study drug will continue to be followed through 28 days after their last dose.

8.4 Stopping Rule

8.4.1 Dose-Escalation Stopping Rule

Dose-limiting toxicity (DLT) will be defined generally as clinically significant, severe (Grade 3) AEs occurring in \geq 2 subjects that are determined to be clinically significant and considered related to study drug.

If 2 or more subjects at any time in any cohort (8 total subjects per cohort) have Grade 3 AEs that are determined to be clinically significant and considered to be related to study drug, dosing will be halted within that cohort and no further dose-escalation will occur. If the dose-escalation

stopping rule is met in Cohort 1 (10 mg/kg) all safety data and all available pharmacodynamics will be reviewed and a cohort may be added at a dose at least 50% lower than the 10 mg/kg dose. If the stopping rule is not met after Cohort 1, dose-escalation may proceed up to a maximum of 30 mg/kg. If the dose-escalation stopping rule is met in Cohort 2, all safety data and all available pharmacodynamics will be reviewed and a cohort may be added at a dose a minimum of 30% lower than the Cohort 2 dose. If the stopping rule is not met after Cohort 2, dose-escalation may proceed up to a maximum of 45 mg/kg; however, this cohort may also receive a dose equal to or less than 30 mg/kg based on evaluation of all safety and pharmacodynamic data.

8.4.2 Study Stopping Rule

If any subject experiences a life-threatening AE (Grade 4) that is considered to be related to study drug, further dosing in all enrolled subjects will be suspended until the DEC has evaluated the event and determined the appropriate course of action. At any time during the study, the study may be discontinued if the DEC determines that further drug exposure would pose an undue risk to subjects.

8.4.3 Individual Stopping Rule

Dosing for any individual subject will be discontinued (i.e., no further study drug will be given to that subject) if the subject experiences any study drug-related SAE or any study drug-related non-SAE adverse event that, in the judgement of the Investigator and Medical Monitor suggest that it could be unsafe to administer further study drug to that subject. Additionally, a subject may be discontinued from further treatment with study drug, at the discretion of the Investigator with consultation with the Medical Monitor, if they require a significant increase in dose(s) of anti-pemphigus medication(s) for the management of pemphigus.

9 **STUDY DRUG**

For detailed information regarding SYNT001 preparation and administration, refer to the Pharmacy Manual.

9.1 SYNT001

SYNT001 is provided in vials containing 5 mL SYNT001 (extractable volume) at a nominal concentration of 50 mg/mL. The product is supplied as a liquid at pH 6.5 \pm 0.5. SYNT001 is diluted in Dextrose 5% in Water (D5W) to prepare the solution for infusion. SYNT001 will be infused via IV in 250 mL over 1 hour using a 0.2-micron, inline filter.

Two cohorts of 8 eligible subjects each will receive 5 once-weekly 60-minute infusions of SYNT001 in planned doses of 10 mg/kg or 30 mg/kg. Based on review of safety, PD, and clinical outcomes of these two cohorts, a third cohort of up to 8 subjects may be treated at another dose, with a maximum dose of 45 mg/kg, but may also be lower than 10 mg/kg or between 10 and 30 mg/kg, inclusive.

The specification for host cell DNA in SYNT001 is < 2 pg/mg, the limit of quantitation of the assay. To comply with regulatory guidelines, which specify a maximum level of 10 ng host cell DNA per dose, dosing is limited to 5000 mg of SYNT001. Therefore, at the highest dose possible in this study (45 mg/kg), maximum subject weight will be limited to 111 kg.

9.2 **Cohort Dosing**

Cohorts will be dosed sequentially beginning with Cohort 1. The first 2 subjects will be dosed at least 24 hours apart. A review of the 24-hour safety data for the first subject will be performed to ensure that there are no overt safety concerns before dosing the second subject. A review of the 7-day safety data for the first 2 subjects will be performed prior to dosing the remaining 6 subjects in the cohort. Cohort 2, and Cohort 3 if added, will be dosed per the same schedule

9.3 **Timing of Dosing**

On Days 0, 7, 14, 21, and 28, subjects will receive a 60-minute IV infusion of SYNT001 in the morning. The date and time the dose is administered will be recorded.

9.4 **Identity of Investigational Products**

All supplies of SYNT001 will be supplied by Syntimmune and must be stored refrigerated (2°C to 8°C/36°F to 46°F) in the carton and protected from light, in a securely locked area, accessible to authorized persons only, until needed for dose preparation. Qualified site personnel will

inventory the investigational product received and will maintain records of disposition of the drug, including dates, quantity and use.

9.5 Investigational Product Retention at Study Site

The Investigator (or designee) is responsible for maintaining accurate accountability records of the investigational product throughout the clinical study. All study drug received at the site must be inventoried and accounted for in an accountability log provided by the Sponsor. All dispensing and accountability records will be available for Sponsor review. Study drug accountability will be verified during on-site monitoring visits.

Upon the completion or termination of the study, and upon written authorization from the Sponsor, or its representative, all unused and/or partially used study drug should be returned or destroyed at the investigational site, as specified by Sponsor. It is the Investigator's responsibility to ensure that the Sponsor, or its representative, has provided written authorization that procedures for proper disposal of the study drug have been established, and that appropriate records of the disposal are documented and maintained. No unused study drug may be disposed until fully accounted for by the Sponsor monitor (or designee)

9.6 Warnings and Precautions

Note: Subjects must not receive any vaccinations from within 2 weeks of screening until 2 months after the last dose of study drug.

9.6.1 Infusion Reaction

SYNT001 will be given as an IV infusion over 1 hour. As with all mAbs administered by IV infusion, infusion reactions are possible. In nonclinical testing of SYNT001 in NHPs, clinical observations were limited to infusion reactions due to the immunogenicity of SYNT001 in NHPs. These reactions included transient emesis/vomitus which typically occurred within 1 hour of dosing at all dose groups, but only after the third weekly infusion following the development of ADAs. Transient histamine-type responses were noted 30 minutes post-dose in some animals in all dose groups, but only following the third weekly infusion as above. These reactions were consistent with a histamine reaction (decreased activity, periocular swelling, erythema, facial flushing, eyelids partially/completely closed, and/or generalized weakness). With the exception of vomitus/emesis and red skin discoloration associated with injection or blood draw sites, these observations spontaneously resolved within 1-hour post-dose. Subsequent pretreatment with intramuscular diphenhydramine prevented further histamine-type reactions. All doses of SYNT001 were administered by bolus infusion over approximately 5 minutes in the NHP

studies. However, all of the observed infusion reactions (including vomitus/emesis and histamine-type reactions) associated with ADAs are not at all predictive of what may occur in humans [Bugelski 2004, Ponce 2009] and furthermore, are not considered relevant to predicting responses in humans [ICH S6(R1) 2011].

Typically, infusion reactions to monoclonal antibodies observed in human studies develop within 30 minutes to 2 hours after the initiation of drug infusion, although symptoms may be delayed for up to 24 hours. Most are mild in severity, although severe and even fatal reactions can occur.

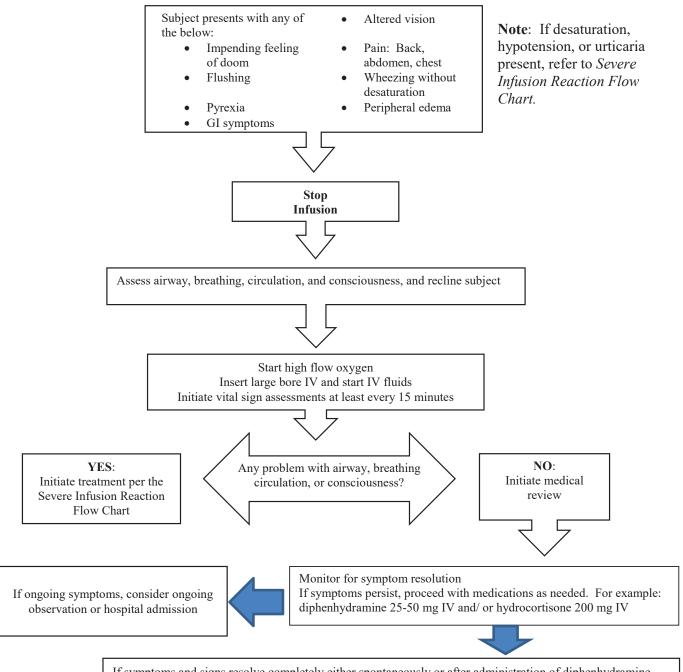
Guidelines for Grading and Management of Allergic or Infusion-Related Reactions

Allergic and/or infusion-related reactions include hypersensitivity reactions and cytokine release syndromes. These reactions are experienced by patients during or within hours of the infusion of monoclonal antibody therapy. Symptoms can include flushing, alterations in heart rate and blood pressure, dyspnea, bronchospasm, back pain, fever, urticaria, edema, nausea, and all types of rashes. Anaphylaxis is recognized as a severe, life-threatening, generalized, or systemic reaction. This is a medical emergency characterized by rapidly developing life-threatening airway and/or breathing and/or circulation problems usually associated with skin or mucosal changes.

Management of Grade 1 infusion reactions include decreasing the rate of infusion by 50% and observing. Symptoms may also be treated as needed with medications such as diphenhydramine, hydrocortisone or acetaminophen.

Management of Grade 2 and higher infusion reactions should include stopping the infusion of study drug. See Figure 1 and Figure 2 for details on the management of Grades 1-2 and Grade 3 or higher infusion reactions. The severity of and management of allergic or infusion-related reactions will be graded and managed using NCI CTCAE Version 4.03 (see Table 6).

Figure 1: Management of Mild (Grade 1) to Moderate (Grade 2) Infusion Reactions



If symptoms and signs resolve completely either spontaneously or after administration of diphenhydramine with or without hydrocortisone, consider rechallenge:

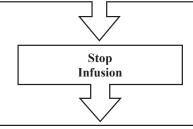
Wait at least 20 minutes following medication administration before commencing rechallenge at an infusion rate of 50% or less of the initial infusion rate or

Consider pre-medicating the subject with the same medication(s) 20-30 minutes in advance of subsequent administrations of SYNT001 and starting infusion at 50% of the planned infusion rate for the first 30 minutes, then returning to the intended infusion rate in the absence of any infusion reaction

Figure 2: Management of Severe (Grade 3 or higher) Infusion Reactions

Subject presents with any of the below:

- Urticaria
- Airway threatened by angioedema
- Angioedema: Lip, mouth, facial swelling
- Respiratory compromise wheezing, dyspnea, stridor or hypoxia (O2 saturation < 90%)
- BP < 90 mmHg SBP or >30% decrease from patient baseline



Start basic life support:

- High oxygen flow
- On bed, head down, legs up
- Large bore IV cannula, 1 L normal saline STAT
- Initiate vital signs at least every 15 minutes



Consider (under medial direction):

Epinephrine 1:1000

• 0.3 mg (0.3 mL) IM into lateral thigh



Airway Threatened: Nebulized epinephrine 1:1000, 3–5 mL (3–5 mg)

Bronchospasm: Nebulized salbutamol 5 mg

(Wheeze or Hypoxia) Consider: Intubation / nebulized epinephrine

Hypotension: Place on cardiac monitor

(Systolic BP <100 mmHg) Further epinephrine 1:1000, 0.3 mg IM and

IV normal saline bolus 20 mL/kg STAT as needed

Have vasopressin on hand



Transfer to Emergency Room/ICU Observe until all symptoms resolved.

Table 5: Grading and Management of Allergic or Infusion-Related Reactions

Adverse Event	Grade					
	1	2	3	4	5	
Infusion- Related Reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids): prophylactic medications indicated for ≤ 24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement, hospitalization indicated for clinical sequelae	Life- threatening consequences; urgent intervention required	Death	
Allergic Reaction	Transient flushing or rash, drug fever < 38.0°C. Intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids): prophylactic medications indicated for ≤ 24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement, hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life- threatening consequences; urgent intervention required	Death	
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticarial; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life- threatening consequences; urgent intervention required	Death	
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids): prophylactic medications indicated for ≤ 24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement, hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life- threatening consequences; pressor or ventilator support indicated	Death	

Abstracted from NCI CTCAE Version 4.03.

9.6.2 Potential Immune Effects

An antibody blocking FcRn is anticipated to have several effects. These include acceleration of catabolism of IgG, but not other immunoglobulin isotypes such as IgA and IgM, leading to dose-dependent decreases in circulating IgG levels by up to an estimated 50% from the baseline levels after a single dose and further decreases after multiple doses up to a 70% to 80% reduction. Based on studies in humans, it is expected that with a single dose, the nadir of this effect will occur approximately 5 days after dosing. The time course of recovery of IgG following dosing in the Phase 1a study suggests that a return to within normal limits occurs within 4 weeks after a single dose and within 4 weeks after multiple doses as shown in NHPs.

Given the normal adult range of IgG of 700 to 1600 mg/dL (in some references), with a mean of 1150 mg/dL, a 50% decrease in the mean would be to 575 mg/dL and a 50% decrease from the low end of the normal range of 700 mg/dL would be to 350 mg/dL. An 80% decrease from baseline after multiple doses would result in IgG levels of 230 mg/dL and 140 mg/dL, respectively. While these levels are in the range found in patients with primary humoral immunodeficiency [Ameratunga 2013], the levels will be transient. Study subjects will be monitored clinically for any infection. Further, commercial IVIG can be given to reverse the low IgG levels in case of a bacterial infection occurring while their IgG levels are decreased.

An antibody blocking FcRn is expected to also down modulate innate and adaptive immunity and the catabolism of IgG-containing immune complexes (IC). Specifically, it is expected that anti-FcRn will promote the clearance of IgG-containing ICs and the effects of these IC on stimulating innate immune cell production of inflammatory cytokines (e.g., IL-12, interferon-γ, and tumor necrosis factor [TNF]) and inhibit the processing and presentation of antigens contained within IC and thus the antigen-specific activation of CD4⁺ and CD8⁺ T-cells. Therefore, subjects with pre-existing conditions that are dependent upon IgG antibodies, such as chronic infections (e.g., HIV, HBV or HCV), will be excluded from this study, as will subjects with active infection in general.

SYNT001 administration could decrease the level of protective antibodies from prior vaccinations. Protective antibody levels for tetanus and varicella-zoster virus (chickenpox) are to be tested in accordance with Section 6.7.3.

10 CONCOMITANT MEDICATION AND TREATMENT

All treatments a subject receives within 14 days prior to enrollment through the end of the study (Day 56) will be documented. Concomitant medication and treatment for co-existing conditions, including those for pemphigus, are permitted if not excluded below. Topical antibiotics are permitted to treat active infections that occur on study. Topical or systemic treatments for oral candidiasis are permitted. Topical lidocaine for transient pain relief is acceptable as needed. Significant increases in anti-pemphigus medications may result in subjects being discontinued from the study. Concomitant treatment that is medically indicated for any AEs the subject experiences during the study are permitted

Use of the following treatments will not be permitted during the study unless otherwise specified:

- Rituximab or other anti-CD20 antibody
- Monoclonal antibodies other than study drug
- Any immunosuppressive drugs apart from corticosteroids, azathioprine, mycophenolate mofetil, or cyclosporine.
- Topical steroids
- Any dietary herbal supplements
- Any investigational drug or device
- Any vaccinations

If over a period of at least two weeks on study drug, a subject on corticosteroids shows the absence of new lesions and significant healing of lesions that existed at study baseline, a slow corticosteroid taper may be started as per the following suggested schedule

- If on > 30 mg of prednisone per day, decrease by 10 mg every two weeks until a dose of 30 mg per day then decrease by 5 mg every two weeks
- If on < 30 mg of prednisone per day, decrease by 5 mg every two weeks

In cases in which concomitant medications are used, details to be recorded include the following: medication name, start date and time, stop date and time, dose, route, frequency, and reason for use. The concomitant medication names are to be coded using the World Health Organization

(WHO) Drug Dictionary (WHO-DD March 2013, Type B2 or later) and classified by anatomical therapeutic chemical (ATC) categories.

11 SAFETY

11.1 Safety Parameters

Clinical and laboratory AEs will be graded using the NCI CTCAE; Version 4.03 (See Appendix A).

Subjects will be monitored throughout the treatment and follow-up period for occurrence of AEs (acute, delayed, and/or cumulative), as well as for changes in clinical status, vital sign measurements, and laboratory data (including PD). Safety parameters to be measured/assessed include PEs, vital sign measurements, hematology, serum chemistries, urinalysis, and ECG.

11.2 Adverse Event Definition

An AE is defined as any untoward medical occurrence in a clinical trial subject associated with the use of a drug, whether considered drug related. An AE can be an unfavorable and unintended sign (e.g., an abnormal laboratory value finding), a symptom, or a disease temporally associated with the use of a drug, without judgment as to causality. An AE can arise from use of the drug (e.g., use in combination with another drug) and from any route of administration, formulation or dose, including an overdose. An AE also includes, but is not limited to, any clinically significant worsening of a pre-existing condition. Examples include:

- Any sign, symptom, physical finding, or laboratory result that has worsened in nature, severity or frequency compared to baseline;
- Reactions from an investigational drug, including those occurring because of an overdose, abuse of the study drug, withdrawal phenomena, sensitivity or toxicity;
- Concurrent illness that was not present or worsens in nature, severity, or frequency compared to baseline;
- Injury or accident; and/or
- Exacerbation of a pre-existing condition.

For data collection, all untoward events that occur after informed consent through 28 days after study drug dosing are to be recorded on eCRFs by the investigational site.

While pregnancy alone is not considered as an AE or SAE, any pregnancy complication(s) should be recorded as an AE(s) or SAE(s) (if applicable). Elective abortions without complications should not be regarded as AEs, unless they were therapeutic abortions (see below). Hospitalization for normal delivery of a healthy newborn should not be considered an SAE. If a female subject becomes pregnant during the conduct of the study, the Investigator must notify the Sponsor according to the procedures provided in Section 11.3.8).

11.3 Evaluating Adverse Events

The Investigator will determine the seriousness, intensity, and causality of an AE associated with the use of the study drug (i.e., events where there is a reasonable possibility that the event may have been caused by the study drug) based on the definitions that follow.

11.3.1 Serious Adverse Events

(Notify Medpace Safety within 24 hours; document on eCRF)

The SAE definition and reporting requirements are in accordance with Title 21 Part Code of Federal Regulations (CFR) 312.32 and the Guidance for Industry and Investigators Safety Reporting Requirements for Investigational New Drug (INDs) and Bioavailability /Bioequivalence Studies.

SAE: An AE is considered "serious" if, in the view of either the Investigator or sponsor, it results in any of the following outcomes:

• <u>Death:</u> This includes any death that occurs while the subject is "on study" as well as any death that occurs within 28 days after study drug administration.

Note: Death is an outcome of an AE, and not an AE. The event(s) that caused death (e.g., illness, accident) is the SAE. Death due to any other cause(s) must also be reported as an outcome of the reportable SAE.

• <u>Life-threatening adverse drug event:</u> An AE or suspected adverse reaction is considered "life threatening" if, in the view of either the Investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

• Inpatient hospitalization or prolongation of existing hospitalization:

In the absence of an AE, the Investigator should not report hospitalization or prolongation of hospitalization. This is the case in the following situations:

- Hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol
- Hospitalization or prolongation of hospitalization is part of routine procedure followed by study center

- Hospitalization for survey visits or annual physicals
- Hospitalization for observation with release within 24 hours

In addition, a hospitalization planned before the start of the study for a pre-existing condition, which has not worsened, does not count as an SAE.

• Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- Congenital anomaly/birth defect
- <u>Important medical event:</u> An event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

11.3.2 Overdose

An overdose is defined as a significant variation from the recommended/scheduled dosage for a product. The dosing for this study will be conducted in a controlled clinical setting and an overdose is not anticipated. However, in the event of an accident, for this study, an overdose of SYNT001 is considered a dose that is two-fold higher than the intended dose for the subject.

11.3.3 Non-Serious Adverse Events

(Document on eCRF)

All other AEs, not fulfilling the previous definitions, are classified as non-serious.

11.3.4 Protocol-Related Adverse Events

AEs that are not test drug related may nevertheless be considered by the Investigator or the Medical Monitor to be related to the conduct of the clinical study. That is, the event may be related to the fact that a subject is participating in the study. For example, a protocol-related AE may be an event that occurs during a screening period or that is related to a procedure required by the protocol.

11.3.5 Assessment of Causality

A medically qualified Investigator must assess the relationship of any AE (including SAEs) to the use of the investigational product, as related or not related, based on clinical judgment and using all available information, and may include consideration of the following factors:

- Possible alternative causes of the AE, including the disease under treatment, pre-existing conditions, concomitant use of other drugs, and presence of environmental or genetic factors
- The temporal association between drug exposure and onset of the AE.
- Whether the manifestations of the AE are consistent with known actions or toxicity of the investigational product.
- The AE resolved or improved with decreasing the dose or stopping use of the investigational product (dechallenge). Judgment should be used if multiple products are discontinued at the same time.

The causal relationship between the study medication and the AE will be assessed using one of the following categories:

Not Related: Factors consistent with an assessment of Not Related include:

- Temporal relationship is lacking (e.g., the event did not occur within a reasonable time frame following administration of the study medication); or
- Other causative factors more likely explain the event (e.g., a pre-existing condition, other concomitant treatments).

Related: Factors consistent with an assessment of Related include:

• There is a positive temporal relationship (e.g., the event occurred within a reasonable time frame following administration of study medication); or

The AE is more likely explained by the investigational product than by another cause (i.e., the AE shows a pattern consistent with previous knowledge of the investigational product or the class of the investigational product)

11.3.6 Recording Adverse Events

All AEs (including SAEs) are to be accurately recorded on the <u>Adverse Event</u> page of the subject's eCRF. The severity of each AE will be graded using the NCI CTCAE, Version 4.03. The date of onset as well as the end date of the event also should be recorded or the event should be entered as "ongoing". In addition, the method used to treat the AE and the outcome of the AE also will be noted. The Investigator will assess the relationship of the event to study drug.

11.3.7 Planned Hospitalization

A hospitalization planned by the subject prior to the first dose of study medication is considered a therapeutic intervention and not the result of a new SAE and should be recorded as medical

history. If the planned hospitalization or procedure is executed as planned, the record in the subject's medical history is considered complete. However, if the event/condition worsens during the trial, it must be reported as an AE.

11.3.8 Reporting Pregnancies

If a female subject or the female partner of a male subject becomes pregnant during the course of the study, the Investigator must report the pregnancy to the Medpace Safety using the **Pregnancy Reporting Form** within **24 hours** of becoming aware of the event. The Investigator must obtain consent to collect pregnancy information (including the status of the newborn, if applicable).

If some of the information required for completion of the Pregnancy Reporting Form is unavailable at the time of the initial report, follow-up reports will be completed and submitted within 24 hours of becoming aware of the new information. Any pregnancy will be followed through delivery for the observation of any SAEs. Any SAE that occurs during pregnancy must be recorded on the SAE report form in the EDC system (e.g., maternal serious complications, therapeutic or spontaneous abortion, ectopic pregnancy, stillbirth, neonatal death, congenital abnormality, birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs (See Section 11.3.9).

11.3.9 Serious Adverse Event Reporting

11.3.9.1 Governing Regulatory Requirements

Compliance with this request for prompt reporting is essential in that the sponsor is responsible for informing the US Food and Drug Administration (FDA) and other regulatory authorities as well as all other participating Investigators of the event.

Under FDA ruling (US Code of Federal Regulations, Title 21 CFR Part 312.32) and the ICH Guidelines for Clinical Safety Data Management Definitions and Standards for Expedited Reporting, the sponsor is required to submit written documentation, in the form of a safety report, detailing:

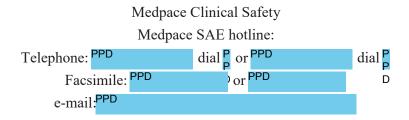
- Any event associated with the use of the drug, that is both serious and unexpected, or
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.

Written submission must be made by the sponsor to the FDA and the IRBs as soon as possible and in no event later than 15 calendar days after the sponsor's initial notification of the event. The sponsor shall also inform all Investigators.

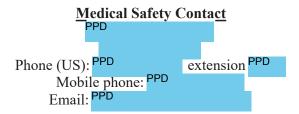
11.3.9.2 Time Frame for Reporting

Any death, SAE, pregnancy, or unexpected (and severe) AE experienced by the subject after informed consent or within 28 days of receiving study drug, regardless of relationship to study drug, or any death that occurs more than 28 days after receiving study drug, and is believed to be study drug related, must be promptly reported (within 24 hours of the Investigator becoming aware of the event) by telephone or electronic transmission to the sponsor (or designee).

Contact information for **SAE** reporting:



Additionally, the Investigator will be able to contact the **Medical Monitor**:



11.3.9.3 Information to be Provided by the Investigator

SAEs must be recorded on the SAE form in the EDC system. This requirement includes all SAEs that occur after informed consent and through 28 days after study drug dosing, and in addition, any SAE that are assessed as related to study treatment by the Investigator, even if the SAE occurs more than 28 days after study drug dosing.

The minimum information required for SAE reporting includes identity of Investigator, site number, subject number, an event description, SAE term(s), onset date, the reason why the event is serious (i.e., the seriousness criteria) and the Investigator's assessment of the relationship of the event to study treatment. Additional SAE information including medications or other therapeutic measures used to treat the event, action taken with the study treatment due to the event, and the outcome/resolution of the event will be recorded. Paper forms for reporting SAEs will be provided to the study sites as back-up in case the EDC system is not accessible.

In all cases, the Investigator should continue to monitor the clinical situation and report all material facts relating to the progression or outcome of the SAE. Furthermore, the Investigator may be required to provide supplementary information as requested by Syntimmune or designee.

When reporting an SAE, the following additional points should be noted:

When the diagnosis of an SAE is known or suspected, the Investigator should report the diagnosis or syndrome as the primary SAE term, rather than as signs or symptoms. Signs and symptoms may then be described in the event description. For example, dyspnea should not be used as an SAE term if the diagnosis, which caused the dyspnea, is known to be malignant pleural effusion.

- Death should not be reported as an SAE, but as an outcome of a specific SAE, unless the event preceding the death is unknown. In the exceptional case where the events leading to death are unknown, then death may be used as an event term. If an autopsy was performed, the autopsy report should be provided.
- While most hospitalizations necessitate reporting of an SAE, some hospitalizations do not require SAE reporting, as follows:
 - Elective or previously scheduled surgery, e.g., a previously scheduled ventral hernia repair
 - Procedures for pre-existing conditions that have not worsened after initiation of treatment
 - Pre-specified study hospitalizations for observation
 - Events that result in hospital stays of less than 24 hours and that do not require admission, e.g., an emergency room visit for hematuria that results in a diagnosis of cystitis and discharge to home on oral antibiotics
- SAEs must, however, be reported for any surgical or procedural complication resulting in prolongation of the hospitalization.

11.3.10 **Regulatory Reporting**

Syntimmune (or designee) will process and evaluate all SAEs as soon as the reports are received. For each SAE received, Syntimmune will decide as to whether the criteria for expedited reporting have been met.

Syntimmune (or designee) will submit SAEs that meet the criteria for expedited reporting to the regulatory authorities in accordance with local regulations governing safety reporting. Reporting of SAEs by the Investigator to his or her IRB will be done in accordance with the standard operating procedures and policies of the IRB. Adequate documentation must be maintained showing that the IRB was properly notified.

11.3.11 Follow-up Information on a Serious Adverse Event (SAE)

Appropriate diagnostic tests should be performed and therapeutic measures, if indicated, should be instituted. Appropriate consultation and follow-up evaluations should be carried out until the event has returned to baseline or is otherwise explained by the Investigator.

If all required information on the SAE form is not available at the time of the initial report, follow-up information will be completed in the EDC system.

11.4 Other Safety Considerations

11.4.1 Laboratory Data

All laboratory data obtained during the study should be reviewed. Any abnormal value that leads to a change in subject management (e.g., requirement for additional medication or monitoring) or is of clinical significance by the Investigator should be reported as an AE and/or SAE as appropriate, unless this value is consistent with values obtained before entry into the study.

11.4.2 Medication Errors

Any medication error that results in an AE, even if it does not meet the definition of serious, requires reporting within 24 hours to the safety Medical Monitor.

11.4.3 Follow-Up of Adverse Events

Any SAE or AE assessed as related that led to treatment discontinuation (including clinically significant abnormal laboratory values that meet these criteria) and ongoing 28 days after study drug dosing must be followed until either resolution of the event or determination by the Investigator that the event has become stable or irreversible. This follow-up guidance also applies to related SAE that occur more than 28 days after study drug dosing. The status of all other continuing AEs will be documented as of 28 days after study drug dosing. The Investigator will follow all subjects who experience AEs until there is a return to the subject's baseline condition, or until a clinically satisfactory resolution has been achieved. The appropriate follow-up visits must be scheduled and the specific tests repeated or performed as necessary.

Where a diagnosis is possible, it is preferable to report this diagnosis rather than a series of terms (signs/symptoms) relating to the diagnosis.

11.5 Safety Monitoring for Dose Escalation

Following dosing in each cohort, all safety/tolerability data (e.g., PEs, vital signs [including pulse oximetry], clinical safety laboratory tests, ECGs and AE/SAE assessments) as well as any available and relevant PD data collected through Day 42 will be reviewed by the DEC. A decision to escalate to the next cohort will be made. The recommendation may be to continue to the next scheduled dose level, discontinue the study or to modify dosing to a dose less than the current dose or higher than the current dose but lower than the next planned dose.

12 STATISTICAL CONSIDERATIONS

All descriptive and inferential statistical analyses will be performed using the most recently released and available Statistical Analysis System (SAS) software, unless otherwise noted. Missing data will not be imputed unless otherwise stated. All clinical data captured will be provided in data listings. A Statistical Analysis Plan (SAP) and a Pharmacokinetic Analysis Plan (PAP) will be finalized prior to database lock.

12.1 General Design

All data for enrolled subjects will be presented in data listings by subject number.

Continuous data will be described using descriptive statistics: number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Frequencies and percentages will be used for summarizing discrete (categorical) data. When categorical data are presented, the percent will be suppressed when the count is zero to draw attention to the non-zero counts. The denominator for all percentages, unless otherwise specified, will be the number of subjects in the specified analysis population.

12.2 Sample Size Justification

Formal sample size calculations were not performed. The number of subjects was chosen based on feasibility and was considered sufficient to meet the study objectives.

12.3 Statistical Considerations

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP). The SAP may modify the plans outlined in the protocol; any deviations from the previously described statistical plan will be described and justified in an SAP amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate and will be described in the SAP. Methods of handling of missing data for different endpoints will be further specified in the SAP. In general, where individual data points are missing because of insufficient samples, dropouts, or other reasons, the data will be analyzed based on reduced denominators unless specified otherwise in the SAP.

Results will be summarized by cohorts.

12.3.1 Study Populations

Three populations will be employed in the analysis of study data:

- The **intent-to-treat (ITT)** population will consist of all subjects who have received at least one dose of study drug. All safety analyses will be performed on the ITT population.
- The **PK** population will consist of all subjects who receive at least one dose of study drug and have sufficient post-dose blood samples to obtain PK parameters.
- The **PD** population will consist of all subjects who receive at least one dose of study drug and have post-dose PD data available.

Primary safety analyses will be performed on the ITT population. Demographics, subject disposition, and screening and baseline characteristics will be summarized for the ITT, PK, and PD populations, where appropriate.

12.3.2 Subject Accountability, Demographics, and Baseline Characteristics

Subject disposition, demographic information and baseline characteristics will be presented. Any discrepancy between treatment to be given and treatment received will be accounted for in these displays.

12.3.3 Concomitant Medications

Concomitant medications will be coded using WHO Drug Dictionary (WHO-DD March 2013, Type B2 or later) and the data will be summarized and presented in tables and listings.

12.4 Planned PK Analysis

Study drug concentrations will be used to calculate the following PK parameters: $t_{1/2}$, C_{max} , T_{max} , and AUC_{0-24} and $AUC_{0-\infty}$. PK parameters will be determined using noncompartmental method(s). Descriptive statistics of PK parameters for SYNT001 will include mean, SD, coefficient of variation (CV), median, minimum, and maximum. T_{max} will be reported as median and range. All descriptive statistics will be performed on untransformed PK parameters and after log_{10} transformation of PK parameters.

For calculation of mean concentrations and generation of mean concentration-time profiles, all below the limit of quantification (BLQ) values will be set to zero except when an individual BLQ falls between 2 quantifiable values, in which case it will be omitted.

If there are values above the BLQ, but too sparse to allow full analysis, descriptive statistics will be performed on available values.

12.5 Safety Data

Safety observations and measurements include AEs, safety laboratory tests, vital sign measurements, PEs, and ECGs.

Treatment-emergent AEs will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA®; Version 19 or higher) System Organ Class (SOC) and preferred term, classified from verbatim terms. The incidence and percentage of subjects with at least 1 occurrence of a preferred term will be included, using the most severe grade. The number of events per preferred term will also be summarized. Causality (relationship to study treatment) will be summarized separately.

AEs, SAEs, and AEs leading to withdrawal, dose modification, or treatment discontinuation will be listed by subject, cohort, and overall per SOC and preferred terms. Duration of AEs will be determined and included in listings, along with action taken and outcome.

Laboratory results will be summarized by cohort. Incidence of laboratory abnormalities will be summarized. The worst on-study grade after the first dose of study drug will be summarized. Results for variables that are not coded will be presented in the listings as below, within, and above the normal limits of the local laboratory.

Vital sign measurements and change from baseline will be summarized at each scheduled time point by cohort using descriptive statistics.

Arithmetic mean of parameters from triplicate ECG will be calculated first for each participant at each planned time point. Then summary statistics of ECG test parameters (mean of triplicate) and change from baseline to each post-dose time point will be calculated. Shift tables for ECG test result category change (normal, abnormal, clinically abnormal) from pre-dose to each post-dose time point showing number and percentage of subjects with movement between categories will be presented by treatment group. Frequency and percentage of subjects experiencing potential QTc prolongation (QTcF > 450) will be summarized at each time point by cohort.

12.6 Pharmacodynamic/Activity Data

PD results will be summarized by cohort.

12.7 Immunogenicity Data

Immunogenicity results will be summarized by cohort.

12.8 Interim Analysis

No interim analysis is planned. Safety results will be examined for making dose-escalation decisions; no statistical analyses are planned for aiding these dose-escalation decisions.

13 DATA QUALITY ASSURANCE

All data will be entered in a validated electronic data capture system using single data entry. Standard procedures (including following data review guidelines, manual clinical review based on subject profiles, computerized validation to produce queries, and maintenance of an audit file which includes all database modifications) will be followed to ensure accurate data. Clinical personnel will review all data listings for outliers, data inconsistencies, and spelling errors.

During the study, a study site monitor will make site visits to review protocol compliance, compare electronic case report forms (eCRFs) against individual subject medical records, assess drug accountability, and ensure that the study is being conducted using pertinent regulatory requirements. eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that subject confidentiality is maintained. Checking the eCRFs for completeness, clarity and cross checking with source documents is required to monitor the progress of the study. Direct access to source data is also required for inspections and audits, and will be carried out giving due consideration to data protection and medical confidentiality. Each Investigator will have assured Syntimmune of full access to complete source data for study participants and associated necessary support at all times.

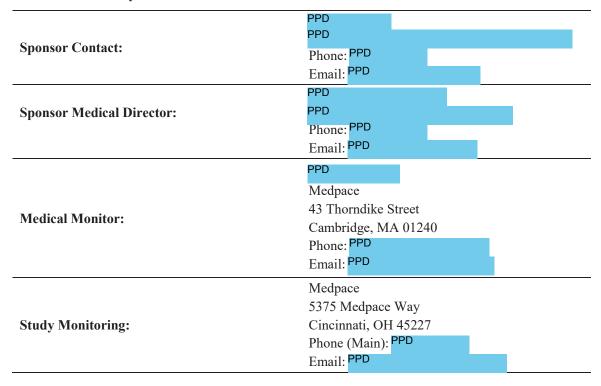
In addition to routine monitoring procedures, audits of clinical research activities in accordance with standard operating procedures (SOPs) may be performed to evaluate compliance with the principles of GCP. A regulatory authority may also wish to conduct an inspection (during the study or even after its completion). If a regulatory authority requests an inspection, the Investigator must immediately inform Syntimmune that this request has been made. Study conduct may be assessed during the study by a Clinical Quality Assurance representative(s) to ensure that the study is conducted in compliance with the protocol. This designee, as well as the site monitor, will be permitted to inspect the study documents (study protocol, eCRFs, investigational product accountability, original study-relevant medical records). All subject data will be treated confidentially. During the clinical study, access will be available to Syntimmune or their designee (e.g., contract research organization [CRO]) to view the eCRFs after completion of the individual sections of the study. Furthermore, the study protocol, each step of the data-recording procedure and the handling of the data as well as the study report may be subject to independent review by a Quality Assurance representative. Clinical site and study audits will be conducted as necessary to assure the validity of the study data.

14 STUDY ADMINISTRATION

14.1 Study Administrative Structure

The study administration structure is provided in Table 6.

Table 6: Study Administrative Structure



14.2 Ethical Conduct of the Study

The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH E6 Tripartite Guideline (January 1997), and in general, be conducted in a manner consistent with the principles described in the Declaration of Helsinki. The Investigator will ensure that the conduct of the study complies with the basic principles of GCP as outlined in the current version of 21 CFR, subpart D, Part 312, "Responsibilities of Sponsors and Investigators", Part 50, "Protection of Human Subjects", and Part 56, "Institutional Review Boards".

14.3 Informed Consent (ICF)

A properly executed, written informed consent document, in compliance with 21 CFR, Part 50 and the ICH guidelines, will be obtained from each subject before the subject is entered into the study and before any study screening procedure is performed that involves risk. Attention will

be directed to the basic elements required for incorporation into the informed consent under US Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a]) and (21 CFR 50.25[b]), as necessary.

Sample ICFs will be supplied to each site. Syntimmune or its designee must review any proposed deviations from the sample ICF. The final IRB-approved document must be provided to Syntimmune for regulatory purposes.

It is the responsibility of the Investigator, or a person designated by the Investigator, to obtain written informed consent from each subject (or the subject's legally authorized representative) participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. In the case where the subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the subject has orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. A copy of the ICF must be provided to the subject or to the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

The eCRF for this study contains a section for documenting informed subject consent, and this must be completed appropriately. Signed ICFs must remain in each subject's study file and must be available for verification by site monitors at any time. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated as necessary. All subjects (including those already being treated) should be informed of the new information, should be given a copy of the revised form, and should give their consent to continue in the study.

14.4 **Institutional Review Board**

This study is being conducted under US IND 128152. This protocol (and any modifications) and appropriate consent procedures must be reviewed and approved by an IRB. This board must operate in accordance with the current federal or local regulations. The Investigator will send a letter or certificate of IRB approval to Syntimmune (or designee) before subject enrollment and whenever subsequent modifications to the protocol are made.

14.5 **Dose Escalation Committee**

The DEC will be responsible for confirming the safety of the investigative product prior to dose escalation, as well as the dose level for each successive cohort. In addition, over the course

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of the study, the DEC will review any drug-related SAEs to determine if modifications to the study or other measures are necessary to ensure the safety of the subjects. The DEC will consist of the Medical Monitor, an Independent Clinical Expert and a Syntimmune Medical Officer. To assist in the safety assessments, the DEC may request that Investigators, other experts, or members within their organizations review the data and participate in the discussions.

14.6 Future Use of Subject Samples

Not all the tissue and blood components obtained during this study may be required for the tests that are part of the clinical trial. Available samples may be used for additional research. This research will help to understand disease subtypes, drug response and AE, and possibly identify new drug targets or biomarkers that predict subject response to treatment. The use of the samples for internal research will be done using the guidelines defined by the FDA guidance for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individual Identifiable (issued 25 April 2006) and the European Medicines Agency (EMA) Reflection Paper on Pharmacogenetic Samples, Testing and Data Handling (Doc. Ref.

EMEA/CHMP/PGxWP/201914/2006; 15 November 2007). If a subject requests destruction of their tissue and blood samples and the samples have not yet been de-identified, Syntimmune will destroy the samples as described in this FDA guidance. Syntimmune will notify the Investigator in writing that the samples have been destroyed.

15 CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications to ongoing studies must be made only after consultation between a Syntimmune representative and the Investigator. Protocol modifications will be prepared, reviewed, and approved by Syntimmune representatives.

All protocol modifications must be submitted to the IRB for information and approval in accordance with local requirements, and to regulatory agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study subjects, or when the change involves only logistical or administrative aspects of the trial (e.g., change in site monitor, change of telephone number).

16 CONDITIONS FOR TERMINATING THE STUDY

Syntimmune has the right to terminate the study at any time. In terminating the study, Syntimmune and the Investigator will ensure that adequate consideration is given to the protection of the subjects' interests.

17 STUDY DOCUMENTATION, CRFS, AND RECORD KEEPING

17.1 Investigator's Files and Retention of Documents

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into 2 separate categories as follows: (1) Investigator's study file and (2) subject clinical source documents.

The Investigator's study file will contain the protocol and protocol amendments, eCRFs, query forms, IRB and governmental approval with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Subject clinical source documents (usually predefined by the project to record key efficacy and safety parameters independent of the eCRFs) may include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalogram, X-ray, pathology and special assessment reports, signed ICFs, consultant letters, and subject screening and enrollment logs. The Investigator must keep these 2 categories of documents on file for at least 2 years following the marketing application approval date for the study treatment and for the indication being investigated or for 2 years after the development program is discontinued and the FDA notified. After that period, the documents may be destroyed subject to local regulations with prior written permission from Syntimmune. If the Investigator wants to assign the study records to another party or move them to another location, Syntimmune must be notified in advance.

If the Investigator cannot guarantee the archiving requirement at the study site for any or all of the documents, special arrangements must be made between the Investigator and Syntimmune to store these in a sealed container outside of the study site so that they can be returned sealed to the Investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the study site.

17.2 Source Documents and Background Data

Investigators must maintain adequate and accurate source documents on which the eCRFs for each subject are based. They are separate and distinct from the eCRFs.

These records include detailed notes on the following:

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- Medical history
- Date and time of informed consent with Health Insurance Portability and Accountability
 Act (HIPAA) authorization either contained in the ICF or presented to the subject
 candidate as a standalone document
- Description of the complete consenting process
- The basic identifying information that linked the subject's medical record with the eCRFs
- The results of all diagnostic tests performed, diagnoses made, therapy provided, and any other data on the condition of the subject
- The medical condition of the subject during their involvement in the study
- All AEs
- The subject's exposure to the study medication
- The subject's exposure to any concomitant therapy
- All relevant observations and data on the condition of the subject throughout the trial
- Justification for all entries in the subject's eCRF

A subject log of all potentially eligible subjects considered, but not consented, for obvious deviations from the entry criteria, will be kept at each site. The log will contain subjects' initials, diagnosis, eligibility, or, if not eligible, reason for not consenting. All consented subjects will be logged, regardless of whether they ultimately enroll.

Upon request, the Investigator will supply Syntimmune with any required background data from the study documentation or clinic records. This is particularly important when eCRFs are illegible or when errors in data transcription are suspected. In case of special problems or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

17.3 Audits and Inspections

The Investigator should understand that source documents for this study should be made available to appropriately qualified personnel from Syntimmune (or designee), or to health authority inspectors after appropriate notification. The verification of the eCRF data must be by direct inspection of source documents.

17.4 Electronic Case Report Forms

Clinical trial data for this study will be captured on eCRF designed for computer processing and analysis. This computerized system will be validated and compliant with 21 CFR Part 11. Corrections to data will be made using 21 CFR Part 11, Electronic Records; Electronic Signatures. If corrections are made after review and sign-off by the Investigator, he/she must be aware of the changes and provide written acknowledgement. There will also be an electronic audit trail. Corrections on paper CRFs must be initialed and dated by the person making the change. The Investigator agrees to provide all information requested on the eCRF in an accurate manner using instructions provided. The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to Syntimmune in the eCRF and in all required reports.

An eCRF is required to be submitted for every subject who receives any amount of study drug. This includes submission of retrievable data on subjects who withdraw before completion of the study. Prior to submission, eCRFs must be reviewed for completeness and accuracy, and signed and dated where either indicated, by the Principal Investigator or authorized delegate from the study staff. If a subject stops treatment or terminates from the study, the dates and reasons must be noted on the eCRF.

18 MONITORING THE STUDY

It is understood that the responsible Syntimmune site monitor (or designee) will contact and visit the Investigator regularly and will be allowed on request to inspect the various records of the trial (eCRFs and other pertinent data) if subject confidentiality is maintained in accordance with local requirements.

It will be the site monitor's responsibility to inspect the eCRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The site monitor should have access to laboratory test reports and other subject records needed to verify the entries on the eCRF. The Investigator (or designee) must agree to cooperate with the site monitor to ensure that any problems detected during these monitoring visits are resolved.

19 CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The Investigator must ensure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On eCRFs or other documents submitted to Syntimmune, subjects should be identified by an identification code and not by their names. The Investigator should keep a subject enrollment log showing codes, names, and addresses. The Investigator should maintain documents not for submission to Syntimmune (e.g., subjects' written consent forms) in strict confidence.

Authorized regulatory officials and Syntimmune personnel (or their representatives) will be allowed full access to inspect and copy the records. All study drugs, subject bodily fluids and tissue, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by Syntimmune.

The Principal Investigator also agrees that all information received from Syntimmune, including but not limited to the IB, this protocol, eCRFs, the INDs, and any other study information remain the sole and exclusive property of Syntimmune during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The Principal Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

20 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. The Investigator agrees that any manuscript or abstract they author may be published only after receiving written permission from Syntimmune.

If Syntimmune coordinates a publication or presentation of study results from all study sites, the participation of Investigator or other representatives of study site as a named author shall be determined in accordance with Syntimmune policy and generally accepted standards for authorship.

21 REFERENCES

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Appendix A: NCI CTCAE, Version 4.03

Appendix B: Pemphigus Disease Area Index (PDAI)

Pemphigus Disease Area Index (PDAI)

Skin	Activity		Damage
Anatomical Locatio	Erosion/Blisters or new erythema		Post-inflammatory hyperpigmentation or erythema from resolving lesion
	0 absent 1 1-3 lesions, up to one >2 cm in any diameter, none > 6 cm 2 2-3 lesions, at least two > 2 cm diameter, none > 6 cm 3 >3 lesions, none > 6 cm diameter 5 >3 lesions, and/or at least one >5 cm diameter of cm diameter of cm diameter of cm diameter or entire area		0 absent 1 present
Ears			
Nose			
Rest of the face			
Neck			
Chest			
Abdomen			
Back, buttocks			
Arms			
Hands .			
Legs			
Feet			
Genitals			/12
Total skin	/120		II nz
Scalp			I Book in governotory
Scalp	Erosion/Blisters or new erythema		Post-inflammatory hyperpigmentation or erythema from resolving lesion
	0 absent 1 in one quadrant 2 two quadrants 3 three quadrants 4 affects whole skull 10 at least one lesion > 6 cm		0 absent 1 present
Total Scalp (0-10)			11 /1
Mucous mer	nbrane		ľ
Anatomical Location	Erosion/Blisters		
	0 absent 1 1 lesion 2 2-3 lesions 5 >3 lesions or 2 lesions >2 cm 10 entire area	Number lesions if ≤ 3	
Eyes			
Nose		\sqcup	
Buccal mucosa			
Hard palate		\vdash	
Soft palate		\vdash	
Upper gingiva		\vdash	
Lower gingiva		\vdash	
Tongue		\vdash	
Floor of mouth		\vdash	
Labial bucosa		\vdash	
Destarias abas se			I
Posterior pharynx		 	
Posterior pharynx Anogenital Total Mucosa	/120		

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Syntimmune, Inc.

SUMMARY OF CHANGES TO CLINICAL STUDY PROTOCOL

A Phase 1b, Multicenter, Open-Label, Safety, Tolerability, and Activity Study of SYNT001 in Subjects with Chronic Pemphigus (Vulgaris or Foliaceus)

Protocol Number: SYNT001-103

IND Number: 132727

Study Drug: SYNT001

Sponsor: Syntimmune, Inc.

257 Park Avenue South

15th Floor

New York, NY 10010

PPD **Medical Monitor:**

43 Thorndike Street, Cambridge, MA 01240

Phone: PPD extension PPD

Mobile: PPD

Original Protocol: 28 January 2017 **Amendment 1.1** 21 March 2017

Confidentiality Statement

The information contained herein is confidential and the proprietary property of Syntimmune, Inc. and any unauthorized use or disclosure of such information without the prior written authorization of Syntimmune is expressly prohibited.

SUMMARY

The SYNT001-103 protocol has been amended with administrative changes as follows:

- Removal of Anti-desmoglein (1&3) antibody testing on Day 28 from the Study Assessments table.
- Total blood draw for subjects completing the study at Day 56 updated to approximately
 311 mL in Section 6.7
- Corrected format and reference for the Pemphigus Disease area Index (PDAI) in Appendix B

SPECIFIC CHANGES

Text deletions are shown using strike through font; additions in *italic font*.

SECTION 1, STUDY SYNOPSIS

Table 1, Study Assessments

Anti-Dsg (1&3) antibody titer: 'X' removed from Day 28 box. Incorrectly included in the Study Assessments Table.

SECTION 6 STUDY PROCEDURES

Section 6.7, Clinical Laboratory Measurements

Laboratory testing (hematology, urinalysis, serum chemistry, virology, serology, pregnancy tests, PD samples, PK samples, and anti-drug antibody samples) will be performed using established methods by a central laboratory. Safety laboratory panels are defined as listed in Table 3. Blood and urine samples for hematology, serum chemistry, and urinalysis will be prepared using standard procedures. Results will be provided to the Investigator. Aliquots from the PK, biomarker and anti-drug antibody samples may be retained as back-up for additional testing as necessary. Subjects will be in a seated or supine position during blood collection. Full clinical safety lab draws will be collected at Screening and on Days 0, 7, 14, 21, 28, 33, 42 and 56. The total blood draw for each subject who completes the study at Day 56, will be approximately 308 311 mL. Please refer to the Laboratory Manual for more information

APPENDIX B:

Pemphigus Disease Area Index (PDAI)

Replaced PDAI form with an updated version as provided by University of Pennsylvania

Syntimmune, Inc.

CLINICAL STUDY PROTOCOL

A Phase 1b, Multicenter, Open-Label, Safety, Tolerability, and Activity Study of SYNT001 in Subjects with Chronic Pemphigus (Vulgaris or Foliaceus)

Protocol Number: SYNT001-103

IND Number: 132727

Study Drug: SYNT001

Sponsor: Syntimmune, Inc.

257 Park Avenue South

15th Floor

New York, NY 10010

Medical Monitor: PPD

43 Thorndike Street, Cambridge, MA 01240

Phone: PPD extension PPD

Mobile: PPD

Original Protocol:18 January 2017Amendment 1.1:21 March 2017Amendment 2.012 April 2017

Confidentiality Statement

The information contained herein is confidential and the proprietary property of Syntimmune, Inc. and any unauthorized use or disclosure of such information without the prior written authorization of Syntimmune is expressly prohibited.

SPONSOR SIGNATURE

I have read and approve this protocol. My signature, in conjunction with the signature of the Investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonisation Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), and the ethical principles that have their origins in the Declaration of Helsinki.

PPD	
	13-4-2017
	Date of Signature
	(DD Mm YYYY)

PROCEDURES IN CASE OF EMERGENCY

Serious Adverse Events

Any death, serious adverse event (SAE)* occurring in a subject while receiving study drug or within 7 days of receiving study drug, even though the event may not appear to be study drug related, must be promptly reported (within 24 hours) by telephone or electronic communication to the sponsor (or designee).

Emergency Contact Information

For SAE reporting:		For any other questions or to contact the Medical Monitor:
Medpace Clinical Safety		PPD
Medpace SAE hotline:		PPD
Telephone: PPD	dial P or PPD	Mobile phone: PPD Office phone: PPD ext. PPD
PPD dial P	D	Office phone: PPD ext. PPD
Facsimile: PPD	or PPD	
PPD		

SAE CRITERIA

- * A <u>serious adverse event</u> (SAE) is any untoward medical occurrence that at any dose results in any of the following outcomes, regardless of relationship to study drug (see Section 11.3.1, Serious Adverse Events for additional information):
 - Death
 - Life-threatening adverse drug event
 - Inpatient hospitalization or prolongation of existing hospitalization
 - A persistent or significant disability/ incapacity
 - A congenital anomaly/birth defect
 - An important medical event that may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Syntimmune, Inc.

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Confidential and Proprietary

Amendment 2.0 Final 12 April

INVESTIGATOR SIGNATURE

I have read and approve this protocol. My signature, in conjunction with the signature of the sponsor, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonization Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), and the ethical principles that have their origins in the Declaration of Helsinki.

Nothing in this document is intended to limit the authority of a physician to provide emergency

medical care under applicable regulations.	
Investigator Signature	Date of Signature (DD Mm YYYY)
Name of Investigator (please print)	

1 SYNOPSIS

Study title	A Phase 1b, Multicenter, Open-Label, Safety, Tolerability, and Activity Study of SYNT001 in Subjects with Chronic Pemphigus (Vulgaris or Foliaceus)
Protocol number	SYNT001-103
Number of study centers	Approximately 10 (US)
Clinical phase	Phase 1b
Study background	SYNT001, a humanized, affinity-matured IgG4-kappa monoclonal antibody (mAb), blocks IgG and IgG immune complex (IC) interactions with the neonatal Fc receptor (FcRn) and thereby the major functions of FcRn in protecting IgG and IgG immune complexes from degradation and their role in downstream signaling events. Specific and high affinity blockade of FcRn with SYNT001 has been shown to increase the catabolism of IgG and IgG IC in healthy volunteers. This predicts that SYNT001 will also accelerate degradation of endogenous circulating IgG autoantibodies and IgG-antigen IC specifically involved in the pathogenesis of autoimmunity. Blocking FcRn interactions with IgG containing immune complexes further predicts that SYNT001 will have consequences for innate and adaptive cellular immunity. In the first instance, blocking multimeric IgG IC interactions with FcRn within antigen presenting cells will result in inhibition of IC-stimulated inflammatory cytokine production and release by these cells. In addition, as FcRn determines the intracellular itinerary of IgG immune complexes within and among compartments important in cellular immunity, it is further anticipated that SYNT001 will block antigen processing and presentation of antigens contained within IC that otherwise lead to CD8+ and CD4+ T cell activation. Thus, SYNT001 will specifically target immune functions associated with IgG and IC that are involved in many autoimmune conditions and dismantle their ability to cause disease. SYNT001 targets mechanisms contributing to pathology in a variety of IgG-mediated autoimmune disorders, including warm antibody autoimmune hemolytic anemia (WAIHA), pemphigus, and chronic inflammatory demyelinating polyneuropathy (CIDP). While current treatments for certain autoimmune disorders including chronic steroids, immunosuppressants, intravenous immunoglobulin (IVIG), plasmapheresis, and anti-CD20 monoclonal antibodies (mAbs), such as rituximab, can be effective, they are frequently associated with significant adverse effects, a

Protocol SYNT001-103

Study rationale	pathogenic role in the mucosal and cutaneous manifestations in patients with pemphigus. Administration of SYNT001, leading to a significant decrease in total IgG, and thereby a corresponding decrease in the level of the pathogenic autoantibodies as well as the ICs to which they are associated, should lead to a decrease in the mucosal and cutaneous manifestations in subjects with pemphigus. Moreover, the ability of SYNT001 to reduce circulating immune complexes (CICs) and the associated innate and adaptive immune responses may allow for further sustained disease modification. This study is being conducted to further evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity of intravenous (IV) SYNT001 as well as its effects on pemphigus disease activity	
	markers.	
Study objectives	Primary objective To evaluate the safety and tolerability of 5 once-weekly IV infusions of SYNT001 at different dose levels in subjects with chronic pemphigus (vulgaris or foliaceus)	
	Secondary objectives	
	 To determine the PK of SYNT001 following 5 once-weekly 1-hour IV infusions at different dose levels To assess the effect of 5 once-weekly doses of SYNT001 at different dose levels on the following PD biomarkers: Immunoglobulins: IgG, IgG subtypes (IgG1-4), IgA, IgM Albumin 	
	• To assess the effect of 5 once-weekly doses of SYNT001 at different dose levels on the following disease activity markers:	
	 Serum anti-desmoglein (Dsg) (1 and 3) antibody levels Pemphigus Disease Area Index (PDAI) 	
	To assess immunogenicity (anti-SYNT001 antibodies)	
	Exploratory objectives	
	 To assess the effect of 5 once-weekly doses of SYNT001 at different dose levels on the following biomarkers, including: 	
	 Serum anti-epithelial cell antibody (AECA) levels by indirect immunofluorescence 	
	 Circulating immune complexes (CIC) 	
	o Complement component 3 (C3)	
	 Exploratory biomarkers (FCGR2A (single nucleotide polymorphism- SNP), RNAseq, urine IgG) 	

Immune phenotyping by flow cytometry for CD3⁺CD4⁺ T, CD3⁺CD8⁺ T, monocytes, NK cells and B cells SYNT001 levels in skin biopsies (optional)

To characterize corticosteroid use during the study

Study design

Phase 1b, multicenter, open-label, safety, tolerability, and activity study

Methodology

Two cohorts of 8 eligible subjects each will receive 5 once-weekly 60-minute infusions of SYNT001 in planned doses of 10 mg/kg or 30 mg/kg. Based on review of safety, PD, and clinical outcomes of these 2 cohorts, a third cohort of up to 8 subjects may be treated at another dose, with a maximum dose of 45 mg/kg, but may also be lower than 10 mg/kg or between 10 and 30 mg/kg, inclusive.

Cohort	No. of subjects	Dose
1	8	SYNT001 10 mg/kg
2	8	SYNT001 30 mg/kg

Cohorts will be dosed sequentially beginning with Cohort 1. The first 2 subjects will be dosed at least 24 hours apart. A review of the 24-hour safety data for the first subject will be performed to ensure that there are no overt safety concerns before dosing the second subject. A review of the 7-day safety data for the first 2 subjects will be performed prior to dosing the remaining 6 subjects in the cohort. This evaluation will include a review of AE/SAE reports, vital sign assessments, physical examinations, ECGs, and clinical laboratory testing. The seriousness, severity, and relatedness of AEs/SAEs will also be considered in the safety evaluation. Safety data will be reviewed on a continuous basis throughout the study. All safety data and any available and relevant PD data through Day 42 (2 weeks after the last subject's last dose in Cohort 1) will be reviewed by a dose escalation committee before Cohort 2 is initiated. Escalation to Cohort 2 will proceed if there are no concerning safety signals and the review of available and relevant PD data supports advancing to a higher dose. The dose for Cohort 2 will be finalized after review of the safety and PD data, but will not exceed 30 mg/kg. Cohort 2 and Cohort 3, if added, will be dosed per the same schedule as Cohort 1.

On days where study drug is administered, vital sign and pulse oximetry measurements will be collected immediately prior to the infusion; 15, 30, and 45 minutes after the start of the infusion; at completion of the infusion; and 30 minutes, 1 hour and 2 hours following completion of the infusion.

On Days 0 and 28, PK blood samples will be collected prior to infusion start and then over the subsequent 48 hours. Subjects will remain at the clinic through the 6-hour PK sample collection and will return to the clinic for the 24- and 48-hour collections. Additional samples will be collected on Days 5 and 33.

On Day 0 photographs will be taken of active lesions. Follow-up photographs will be taken of the same areas on Days 33, 56, 84 and 112. If a subject begins a steroid taper, additional photographs will be taken at the clinic visit during which the decision to begin the taper is made.

Subsequent visits will occur on Days 1, 2, 5, 7, 12, 14, 19, 21, 28, 29, 30, 33, 42 and 56 for safety assessments, study drug dosing, sample collections, and other study procedures.

Subjects will return to the clinic on Days 84 and 112 for follow-up visits. Subjects whose total IgG is not within 30% of their Day 0 baseline value and not above 500 mg/dL at the Day 112 visit will be referred for further management.

See Table 1 for a schedule of all study events. To assess safety and tolerability, subjects will undergo physical examinations (PEs; including weight), vital sign measurements, clinical (safety) laboratory tests, adverse event (AE) assessments, concomitant medication assessments, and electrocardiograms (ECG).

Number of subjects

Approximately 16; two cohorts of 8 subjects each. An additional cohort of up to 8 subjects may be enrolled. Subjects who withdraw for any reason other than an AE and who do not receive study drug or have only received one dose of study drug may be replaced, up to one subject per cohort. The maximum number of subjects who may be enrolled in this study is 27 (24 + up to 3 replacements, as necessary). Within each dosing cohort, no more than 3 subjects with pemphigus foliaceus may be enrolled.

Diagnosis and main entry criteria

Inclusion criteria:

Subjects must meet the following criteria to be included:

- 1. Willing and able to read, understand and sign an informed consent form;
- 2. Male or female ≥ 18 years of age at the time of screening;
- 3. Documented diagnosis of pemphigus vulgaris or foliaceus based on all 3 of the following criteria:
 - a. Documented clinical history consistent with pemphigus vulgaris or foliaceus (clinical presentation defined as mucosal and/ or skin lesions);
 - b. Presence of Anti-Dsg 1 or 3 antibodies above the upper limit of normal;
 - c. History of at least one positive tissue-based test (e.g., biopsy, direct immunofluorescence [DIF])
- 4. Active disease: Lesions lasting > 2 weeks, and 3 active lesions in skin or mucosa or 2 active lesions with at least one being a skin lesion > 1 cm diameter:
 - a. If treated with rituximab or other anti-CD20 antibodies, last dose
 12 months prior to screening;

- b. If being treated with other immunosuppressants (i.e., azathioprine, mycophenolate mofetil or cyclosporine), must be on stable dose (< 10% change in dose) for 6 weeks prior to screening;
- c. If being treated with corticosteroids, must be $\leq 1 \text{mg/kg/day}$ and stable (< 10% change in dose) for 2 weeks prior to screening;
- d. Allowed topical therapies for pemphigus lesions upon entering the study include petroleum jelly or Aquaphor® for the skin or chlorhexidine for the mouth
- 5. Body mass index (BMI) $18.5 35.0 \text{ kg/m}^2$;
- 6. Has a negative urine pregnancy test (for women of childbearing potential) documented prior to the first dose of study drug;
- 7. Females of childbearing potential must agree to be abstinent or else use any two of the following medically acceptable forms of contraception (<1% per year failure rate) from the Screening Period through the final study visit: oral contraceptive, condom with or without spermicidal jelly, diaphragm or cervical cap with spermicidal jelly, or intra-uterine device (IUD). A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception.
- 8. Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months do not require contraception during the study.
- 9. Males with female partners of childbearing potential, including males who are surgically sterile (post vasectomy), must agree to be abstinent or else use a medically acceptable form of contraception from the screening period through the final study visit.

Exclusion criteria:

Subjects meeting any of the following criteria are to be excluded:

- 1. Subject unable or unwilling to comply with the protocol;
- Active non-hematologic malignancy or history of non-hematologic malignancy in the 3 years prior to screening (exclusive of non-melanoma skin cancer and cervical cancer in situ);
- 3. Positive for HIV or hepatitis C antibody;
- 4. Positive for hepatitis B surface antigen;
- 5. Active infection or history of recurrent infections;
- 6. IVIG use within 60 days of screening;
- 7. Received any cytotoxic (other than azathioprine) or mAb therapy in the 3 months prior to screening;
- 8. Any exposure to an investigational drug or device within the 30 days prior to screening
- Plasmapheresis or immunoadsorption within 60 days of screening

	-				
	10. Cellular therapy at any time prior to screening				
	11. Use of any immunosuppressive drugs apart from corticosteroids,				
	azathioprine, mycophenolate mofetil, or cyclosporine within 3 months of				
	screening				
	12. Serum total IgG < 600 mg/dL;				
	13. Subject has any current medical condition that, in the opinion of the				
	Investigator, may compromise their safety or compliance, preclude				
	successful conduct of the study, or interfere with interpretation of the results				
	(e.g., a significant pre-existing illness or other major comorbidity that the				
	Investigator considers may confound the interpretation of the study results);				
	14. Any vaccination within 2 weeks of screening				
Study drug, dosage,	SYNT001				
and administration	Doses: 10 mg/kg and 30 mg/kg. A third cohort of up to 8 subjects may be treated at another dose, with a maximum dose of 45 mg/kg, but may also be lower than 10 mg/kg or between 10 and 30 mg/kg, inclusive.				
	SYNT001 is provided as a liquid at a nominal concentration of 50 mg/mL. SYNT001 is diluted in Dextrose 5% in Water (D5W) to prepare the solution for				
	infusion.				
	Route of administration: IV in 250 mL over 1 hour				
Control, dose, and	Not applicable				
route of					
administration					
Duration of subject	Up to 126 days (18 weeks): Screening of up to 2 weeks (14 days); Treatment				
participation and	period of 8 weeks (56 days); Follow-up period of 8 weeks (56 days)				
duration of study					

Prohibited Concomitant treatments

All treatments a subject receives within 14 days prior to enrollment through the end of the study will be documented. Concomitant medication and treatment for co-existing conditions, including those for pemphigus, are permitted if not excluded below. Topical antibiotics are permitted to treat active infections that occur on study. Topical or systemic treatments for oral candidiasis are permitted. Topical lidocaine for transient pain relief is acceptable as needed. Significant increases in anti-pemphigus medications will result in subjects being discontinued from the study. Concomitant treatment that is medically indicated for any AEs the subject experiences during the study are permitted.

Use of the following medications will not be permitted during the study unless otherwise specified:

- Rituximab or other anti-CD20 antibody
- Monoclonal antibodies other than study drug
- Any immunosuppressive drugs apart from corticosteroids, azathioprine, mycophenolate mofetil, or cyclosporine
- Topical steroids
- Any dietary herbal supplements
- Any investigational drug or device
- Any vaccinations through Day 56. Following Day 56, subjects may receive vaccinations at the discretion of the Investigator.

If over a period of at least two weeks on study drug, a subject on corticosteroids shows the absence of new lesions and significant healing of lesions that existed at study baseline, a slow corticosteroid taper may be started as per the following suggested schedule

- If on > 30 mg of prednisone per day, decrease by 10 mg every two weeks until a dose of 30 mg per day then decrease by 5 mg every two weeks
- If on < 30 mg of prednisone per day, decrease by 5 mg every two weeks

Safety assessments

Safety assessments include AEs, serious adverse events (SAEs), PEs, vital sign measurements, clinical safety laboratory evaluations, ECGs, and reasons for treatment discontinuations due to toxicity. Safety assessments will be performed at specified time points and prior to discharge from the clinic. Vital sign measurements, including blood pressure, pulse rate, respiratory rate, and temperature will be monitored throughout the study. Pulse oximetry will be monitored during the study drug infusion and for 2 hours following the end of the infusion.

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; Version 4.03) will be used for grading clinical and laboratory AEs.

	The AE reporting period for a subject enrolled in the study begins when the subject provides informed consent and is continued through the last study visit. All AEs that occur in the enrolled subjects during the AE reporting period must be recorded, regardless of the relationship of the AE to study drug. Any known untoward event that occurs beyond the AE reporting period that the Investigator assesses as related to study drug should also be recorded.
Dose-escalation rules	Dose escalation decisions will be made by a Dose Escalation Committee (DEC) and will be based on safety and pharmacodynamic evaluations including but not limited to, dose-limiting toxicities, AEs, SAEs, and total IgG levels. Dose-limiting toxicity (DLT) will be defined generally as severe (Grade 3) AEs occurring in ≥ 2 subjects that are determined to be clinically significant and considered related to study drug.
	If 2 or more subjects at any time in any cohort (8 total subjects per cohort) have Grade 3 AEs that are determined to be clinically significant and considered to be related to study drug, dosing will be halted within that cohort and dose-escalation to a higher dose will not occur. If the dose-escalation stopping rule is met during Cohort 1 (10 mg/kg) all safety data and all available pharmacodynamics data will be reviewed and the cohort may resume (if applicable) or a new cohort may be added, at a dose at least 50% lower than the 10 mg/kg dose. If the stopping rule is not met in Cohort 1 (10 mg/kg), dose-escalation may proceed up to a maximum of 30 mg/kg. If the dose-escalation stopping rule is met for the first time during Cohort 2, all safety data and all available pharmacodynamics data will be reviewed and the cohort may resume (if applicable) or a new cohort may be added at a dose at least 30% lower than the Cohort 2 dose. If the stopping rule is not met in Cohort 2, dose-escalation may proceed up to a maximum of 45 mg/kg; however, this cohort may also receive a dose equal to or less than 30 mg/kg based on evaluation of all safety and pharmacodynamic data.
Study stopping rule	If any subject experiences a life-threatening AE (Grade 4) that is considered to be related to study drug, any further dosing in all enrolled subjects will be suspended until the DEC has evaluated the event and determined the next appropriate course of action. At any time during the study, the study may be discontinued if the DEC determines that further drug exposure would pose an undue risk to subjects.
Individual stopping rule	Dosing for any individual subject will be discontinued (i.e., further treatment with the study drug will not be given) if the subject experiences any study drug-related SAE or any study drug-related non-SAE adverse event that, in the judgement of the Investigator (following consultation with the Medical Monitor, if desired) suggest that it could be unsafe to administer further study drug to that subject. Additionally, a subject will be discontinued from further treatment with

	study drug, at the discretion of the Investigator with consultation with the
	Medical Monitor, if they require a significant increase in dose(s) of anti-
	pemphigus medication(s) for the management of pemphigus.
Pharmacokinetics	The PK of SYNT001 will be evaluated following the first and last (fifth) doses of SYNT001.
	Starting on Days 0 and 28, serum samples will be collected just prior to the start of study drug infusion (pre-dose), at 5 minutes and 2, 4, 6, 24, and 48 hours after the end-of-study drug infusion. Additional samples will be collected on Days 5 and 33. Study drug concentration will be used to calculate the following PK parameters: $t_{1/2}$, C_{max} , T_{max} , AUC_{0-24} , and $AUC_{0-\infty}$.
Pharmacodynamics/ Activity	PD samples will be collected for analysis of IgG (serial assessment of IgG levels to identify C _{min} , T _{min}); IgG1-4 subtype levels; IgA levels; IgM levels; albumin levels; anti-Dsg (1 and 3) antibody levels; serum AECA by direct immunofluorescence; CIC; C3; exploratory biomarkers (<i>FCGR2A</i> SNP, RNAseq, urine IgG, CD3 ⁺ CD4 ⁺ T, CD3 ⁺ CD8 ⁺ T, monocytes, NK cells and B cells).
Immunogenicity	Samples will be collected for immunogenicity analyses on Days 0 (pre-dose), 14, 28, 56, 84 and 112.
Skin biopsy	Optional skin biopsy samples will be collected on Day 0 pre-dose and on Days 1, 2, 14, 33, 56 and 84 to analyze SYNT001 levels.
Photography	Photographs of active lesions will be taken at Day 0. Follow-up photographs of the same areas will be taken on Days 33, 56, 84 and 112. Subjects who begin a steroid taper will have additional photographs taken at the clinic visit during which the decision to begin the taper is made.
Statistical methods	Sample size consideration
	Formal sample size calculations were not performed. The number of subjects was chosen based on feasibility and was considered sufficient to meet the study objectives.
	Data presentations/Descriptive statistics
	Three populations will be employed in the analysis of study data.
	The intent-to-treat (ITT) population will consist of all subjects who have received at least one dose of study drug. All safety analyses will be performed on the ITT population.

- The PK population will consist of all subjects who receive at least one dose of study drug and have sufficient post-dose blood samples to obtain PK parameters.
- The PD population will consist of all subjects who receive at least one dose of study drug and have post-dose PD data available.

Primary safety analyses will be performed on the ITT population. Demographics, subject disposition, and screening and baseline characteristics will be summarized for the PK and ITT populations, where appropriate.

Criteria for evaluation

Objective	Endpoint
Primary	
Safety and tolerability of 5 once- weekly IV infusions of SYNT001 to subjects with pemphigus vulgaris or foliaceus	AEs and clinical (safety) laboratory tests
Secondary	
PK of SYNT001 following a 1-hour IV infusion	PK parameters: $t_{1/2}$, C_{max} , T_{max} , $AUC_{0\text{-}24}$, and $AUC_{0\text{-}\infty}$.
Effect of 5 once-weekly IV doses of SYNT001 on: • Total IgG (IgG1-4), IgA, IgM, and albumin • Serum anti-Dsg (1 and 3) antibodies	Changes in levels of IgG, IgG subtypes (IgG1-4), IgA, IgM, albumin, serum anti-Dsg (1 and 3) antibodies
Assess immunogenicity	Anti-SYNT001 antibodies
Disease Activity	PDAI Scores
Exploratory	,
Effect of 5 once-weekly IV doses of SYNT001 on biomarkers including: • CIC • C3 • Serum anti-epithelial cell antibody (AECA) levels • Exploratory biomarkers (FCGR2A SNP, RNAseq, urine IgG) • Immune phenotyping by flow cytometry	Changes in CIC; C3; AECA levels by indirect immunofluorescence; <i>FCGR2A</i> SNP; RNAseq; urine IgG, CD3+CD4+T, CD3+CD8+T, monocytes, NK cells and B cells; urine IgG levels; changes in blood transcriptome
Concomitant Treatment	Corticosteroid use during the study
SYNT001 levels in skin biopsies	Measures of SYNT001 levels in skin biopsies

Treatment-emergent AEs (TEAEs) will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA®; Version 19 or higher) System Organ Class (SOC) and preferred term, classified from verbatim terms. The incidence and percentage of subjects with at least 1 occurrence of a preferred term will be included, using the most severe grade. The number of events per preferred term will also be summarized. Causality (relationship to study treatment) will be summarized separately.

TEAEs, SAEs, and AEs leading to withdrawal, or treatment discontinuation will be listed by subject, and cohort using SOC and preferred terms. Duration of AEs will be determined and included in listings, along with action taken, and outcome.

Laboratory results will be summarized by time point and cohort. The incidence of laboratory abnormalities will be summarized. The worst on-study grade after the first dose of study drug will be summarized. Results for variables that are not coded will be presented in the listings as below, within, and above the normal limits of the central laboratory. Vital sign measurements will be summarized by cohort at each scheduled time point using descriptive statistics.

Study drug concentrations will be used to calculate the following PK parameters: $t_{1/2}$, C_{max} , T_{max} , and area under the curve (AUC). PK parameters will be determined using non-compartmental method(s). Descriptive statistics of PK parameters for SYNT001 will include mean, standard deviation (SD), coefficient of variation (CV), median, minimum, and maximum. T_{max} will be reported as median and range. All descriptive statistics will be performed on untransformed PK parameters and after log_{10} transformation of PK parameters.

PD results will be summarized by cohort. Descriptive statistics of PD parameters for SYNT001 will include mean, SD, CV, median, minimum, and maximum.

Immunogenicity results will be summarized by cohort. Descriptive statistics will include mean, SD, CV, median, minimum, and maximum.

Table 1: Study Assessments

	Screening							Tre	atmen	t Perio	d						ı	Follow-Up
Timepoint (Study Day)	-14 to -1	0	1 (±1 hr)	2 (± 2 hr)	5 ^p (±4 hr)	7 (±6 hr)	12 ^p (±6 hr)	14 (±6 hr)	19 ^p (±6 hr)	21 (±6 hr)	28 (±6 hr)	29 (±1 hr)	30 (±2 hr)	33 (±4 hr)	42 (±3 days)	56 (±5 days)	84 (±5 days)	112 (±5 days) or ET Visit
Informed Consent	X																	
Demographics/Medical History	X																	
Inclusion/Exclusion	X																	
Physical Examination ^a	X	X				X		X		X	X				X	X	X	X
Vital Signs ^b	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pulse Oximetry ^c		X				X		X		X	X							
Clinical Safety Labs ^d	X	X				X		X		X	X			X	X	X	X	X
Pregnancy test ^e	X	X														X		X
Hepatitis & HIV Screen	X																	
12-Lead ECG ^f	X	X					X				X					X		
Tetanus & VZV antibodies		X														X	X	X
PDAI Score		X				X		X		X	X			X	X	X	X	X
PK Sampling ^h		X	X	X	X						X	X	X	X				
Immunogenicity ⁱ		X						X			X					X	X	X
Study Drug Administration ^j		X				X		X		X	X							
Immunoglobulins (IgG, IgA, IgM) and IgG subtypes (IgG 1-4) ^k	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Xq
CIC		X			X	X	X	X	X	X	X			X	X	X	X	X
Anti-Dsg (1 & 3) antibody titer	X	X				X		X						X		X	X	X
C3 and AECA ¹		X						X						X		X	X	X
FCGR2A ^m		X																
RNAseq ^m		X						X						X		X	X	X
Urine IgG ^m		X						X						X		X	X	X
Immune phenotyping ⁿ		X									X					X		
Optional Skin Biopsy		X	X	X				X						X		X	X	
Photography ^o		X												X		X	X	X
Adverse Events					To be	e collec	ted fron	ı the da	te that t	the ICF	is sign	ed throi	igh the i	ast study	visit			
Concomitant Medications					To be	e collec	ted fron	n within	14 day	s prior	to Day	0 throu	gh the l	ast study	visit			

ECG = electrocardiogram; ET= Early Termination; HIV = human immunodeficiency virus; ICF = informed consent form; PD = pharmacodynamic; PK = pharmacokinetic; VZV = varicella-zoster virus

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- a: Complete PE, including weight, to be performed. Height and BMI will be additional assessments conducted at screening.
- b: **Vital sign** measurements (sitting blood pressure, heart rate, respiratory rate, and oral temperature) to be obtained after 5 minutes of seated rest. Any abnormal measurements are to be repeated after 5 minutes of rest. On Days 0, 7, 14, 21, and 28 vital sign measurements will be collected immediately prior to the infusion; 15, 30, and 45 minutes after the start of the infusion; at completion of the infusion; and 30 minutes, 1 hour and 2 hours following completion of the infusion.
- c: **Pulse oximetry:** On Days 0, 7, 14, 21, and 28, pulse oximetry to be measured immediately prior to the infusion; 15, 30, and 45 minutes after the start of the infusion; at completion of the infusion; and 30 minutes, 1 hour and 2 hours following completion of the infusion.
- d: Clinical safety labs: hematology, clinical chemistry, and urinalysis (see Section 6.7 for a complete list). Full clinical safety lab draws will be collected at Screening and on Days 0, 7, 14, 21, 28, 33, 42, 56, 84 and 112.
- e: **Pregnancy test:** To be performed at time of screening and prior to first dose of SYNT001 on Day 0 and on Days 56 and 112 (urine or serum test is acceptable, however, positive urine tests must be confirmed with serum testing.)
- f: Digital 12-lead ECG to be obtained after 5 minutes of rest in the supine position and in triplicate at least 1-2 minutes apart (see Section 6.6 for additional information). On Days 0 and 28 to be obtained 5 minutes after the completion of infusion. Day 12 ECG will be collected only if the visit is conducted at the study site.
- g: **Serology**: Testing at Day 56 will not be done for any subject whose baseline titer is below the level of detection. If the Day 56 results are greater than 30% below the baseline value, or if the subject falls below the level of detection, the subject will be re-tested at Day 84; if still below the baseline value (or level of detection), the subject will be re-tested at Day 112. Any subject whose baseline value for tetanus or VZV was above the detectable level at baseline, and is not within 30% of the baseline value or is below the detectable level by Day 112, will be referred to their primary care physician for further management. See Section 6.7.3 for additional information.
- h: **PK:** Starting on Days 0 and 28, serum samples will be collected just prior to the start of study drug infusion (pre-dose), and at 5 minutes and 2, 4, 6, 24, and 48 hours after the end-of-study drug infusion. Additional samples will be collected on Days 5 and 33. See Section 6.7.4 for additional information.
- i: Immunogenicity: Blood samples will be collected pre-dose when collected on dosing days. Samples will be collected on Days 0, 14, 28, 56, 84 and 112. See Section 6.7.6 for additional information.
- j: Prior to **study drug infusion**, SYNT001 drug product is to be diluted in Dextrose 5% in Water (D5W) to a total volume of 250 mL and administered intravenously over 1 hour using a 0.2-micron, inline filter. See Section 9 for additional information.
- k: Immunoglobulins (IgG, IgA, IgM) and IgG subtypes (IgG 1-4): Collected for measurements of IgG, IgG subtypes (IgG1-4), IgA, and IgM at every visit. On Days 0, 7, 14, 21, and 28, samples are collected prior to infusion of study drug. See Section 6.7.5 for additional information
- 1: Exploratory PD samples (C3 and AECA): collected pre-dose when collected on dosing days. See Section 6.7.5 for complete information.
- m: Samples to be collected and stored; pending review of clinical and pharmacodynamics assessments
- n: Immune phenotyping by flow cytometry for measurement of CD3⁺CD4⁺ T, CD3⁺CD8⁺ T, monocytes, NK cells and B cells
- o: Photographs of active lesions taken prior to first dose on Day 0. Follow-up photographs will be taken at Days 33, 56, 84 and 112. Subjects who begin a steroid taper will have additional photographs taken at the clinic visit during which the decision to begin the taper is made.
- p: Visit Days 5, 12 and 19 may be conducted via at-home nursing in lieu of a subject visit to the study site.
- q: Subjects will return to the clinic on Days 84 and 112 for follow-up visits. Subjects whose total IgG is not within 30% of their Day 0 baseline value and not above 500 mg/dL at the Day 112 visit will be referred for further management.

Table 2: Timing Window Allowances for PK/PD Sampling, ECG, and Vital Sign Measurements

Pharmacokinetic and Pharmacodynamic Sampling	
Timepoint	Tolerance Window
0 hour	−240 min to 0 hour
5 minutes post end-of-infusion	± 5 minutes
2, 4, & 6 hours post end-of-infusion	± 15 minutes
24 hours post end-of-infusion	\pm 60 minutes
48 hours post end-of-infusion	± 120 minutes
ECG	
Timepoint	Tolerance Window
5 minutes post end-of-infusion	± 10 minutes
Vital Signs ^a	
Timepoint	Tolerance Window
0 hour	−240 min to 0 hour
15, 30, and 45 minutes after start of infusion	± 5 minutes
60 minutes after start of infusion	± 10 minutes
30, 60 and 120 minutes post end-of-infusion	± 10 minutes

a. Vital signs to include blood pressure, pulse rate, respiratory rate, oral temperature, and pulse oximetry.

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LIST OF ABBREVIATIONS

ADA Anti-drug antibodies

AE Adverse event

AECA Anti-epithelial cell antibody
ALT Alanine aminotransferase
ANA Antinuclear antibody
AST Aspartate aminotransferase
ATC Anatomical therapeutic chemical

AUC₀₋₂₄ Area under the plasma concentration-time curve from pre-dose (time 0) to 24 hours post-dose

 $AUC_{0-\infty}$ Area under the plasma concentration-time curve from pre-dose (time 0) to infinity

BLQ Below the limit of quantification

BMI Body mass index
BUN Blood urea nitrogen

CAR-T Chimeric antigen receptor and T-cell

CFR Code of Federal Regulations
C3 Complement component 3
CBC Complete blood count

CIC Circulating immune complexes

CIDP Chronic inflammatory demyelinating polyneuropathy

C_{max} Maximum plasma concentration determined directly from the concentration-time profile

CRO Contract research organization

CV Coefficient of variation

CVID Common variable immune deficiency

DEC Dose escalation committee
D5W Dextrose 5% in Water
DIF Direct immunofluorescence
DNA Deoxyribonucleic acid
ECG Electrocardiogram

eCRF Electronic case report form
ESR Erythrocyte sedimentation rate
FcGR2a Fc Gamma R2a receptor
FcRn Neonatal Fc receptor

FDA Food and Drug Administration

GCP Good Clinical Practice

GI Gastrointestinal
HBV Hepatitis B virus
HCV Hepatitis C virus

HIPAA Health Insurance Portability and Accountability Act

HIV Human immunodeficiency virus

IB Investigator's brochure IC Immune complex

ICF Informed consent form

ICH International Conference on Harmonization

IgA Immunoglobulin A
IgG Immunoglobulin G
IgG1-4 Immunoglobulin G1-G4
IgM Immunoglobulin M
IL-12 Interleukin 12

IND Investigational new drug
IRB Institutional review board

ITT Intent-to-treat
IUD Intrauterine devices

IV Intravenous

IVIG Intravenous immunoglobulin

MedDRA Medical Dictionary for Regulatory Activities

NHL Non-Hodgkin lymphoma
PD Pharmacodynamics
PE Physical examination
PK Pharmacokinetic
RBC Red blood cells
RNAseq RNA sequencing

QTcF Corrected QT interval using Fridericia's formula

SAE Serious adverse event
SAP Statistical analysis plan
SAS Statistical Analysis System

SD Standard deviation

SNP Single nucleotide polymorphism

SOC System Organ Class

SOP Standard operating procedures

SYNT001 A humanized, affinity matured IgG4-kappa monoclonal antibody

 $t_{1/2}$ Half-life

TEAE Treatment-emergent adverse event

T_{max} Observed time to reach peak plasma concentration

TNF Tumor necrosis factor ULN Upper limit of normal

UNS Unscheduled

VZV Varicella-zoster virus

WAIHA Warm antibody autoimmune hemolytic anemia

WHO World Health Organization

WHO-DD World Health Organization Drug Dictionary

2 BACKGROUND AND RATIONALE

SYNT001, a humanized, affinity-matured IgG4-kappa monoclonal antibody (mAb), blocks IgG and IgG immune complex (IC) interactions with the neonatal Fc receptor (FcRn) and thereby the major functions of FcRn in protecting IgG and IgG ICs from degradation and their role in downstream signaling events. Specific and high affinity blockade of FcRn with SYNT001 has been shown to increase the catabolism of IgG and IgG IC in healthy volunteers. This predicts that SYNT001 will also accelerate degradation of endogenous circulating IgG autoantibodies and IgG-antigen IC specifically involved in the pathogenesis of autoimmunity. Blocking FcRn interactions with IgG-containing ICs further predicts that SYNT001 will have consequences for innate and adaptive cellular immunity. In the first instance, blocking multimeric IgG IC interactions with FcRn within antigen-presenting cells will result in inhibition of IC-stimulated inflammatory cytokine production and release by these cells. In addition, as FcRn determines the intracellular itinerary of IgG ICs within and among compartments important in cellular immunity, it is anticipated that SYNT001 will block antigen processing and presentation of antigens contained within IC that otherwise lead to CD8⁺ and CD4⁺ T cell activation. Thus, SYNT001 will specifically target immune functions associated with IgG that are involved in certain autoimmune conditions and dismantle their ability to cause disease.

SYNT001 targets key mechanisms contributing to pathology in a variety of IgG-mediated autoimmune disorders, including warm antibody autoimmune hemolytic anemia (WAIHA), pemphigus, and chronic inflammatory demyelinating polyneuropathy (CIDP).

While current treatments for certain autoimmune disorders, including high-dose steroids, immunosuppressants, intravenous immunoglobulin (IVIG), plasmapheresis, and anti-CD20 monoclonal antibodies (mAbs), such as rituximab, can be effective, they are associated with significant adverse effects, as well as delayed or non-durable responses.

Pemphigus is a rare group of blistering autoimmune diseases that affect the skin and mucous membranes. Autoantibodies have been shown to play an important pathogenic role in the mucosal and cutaneous manifestations in patients with pemphigus. Administration of SYNT001, which significantly decreases total IgG, including a corresponding decrease in the level of the pathogenic autoantibodies and the ICs to which they are associated, may lead to a decrease in the mucosal and cutaneous manifestations in patients with pemphigus. Moreover, the ability of SYNT001 to reduce circulating immune complexes (CICs) and the associated innate and adaptive immune responses may allow for further sustained disease modification.

2.1 **Study Rationale**

This study is being conducted to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity of intravenous (IV) SYNT001 as well as its effects on pemphigus disease activity markers.

2.2 Selection of Doses in this Study

The planned dose levels of SYNT001 for this Phase 1b safety and proof-of-concept study of 10 mg/kg and 30 mg/kg were selected from careful review of the safety, tolerability, and PD effect on total IgG levels after single and repeat dosing of SYNT001 in non-human primates (NHPs), as well as the safety, tolerability, and PD effect on total IgG levels after single ascending doses of SYNT001 in healthy volunteers. In addition, further consideration was given to the desired level of FcRn blockade to achieve suppression of IgG to a range that has been previously correlated with disease remission. Further, we considered the potential effects of inhibiting FcRn function as they relate to immune complex associated innate and adaptive immunity in choosing these dose levels based upon exploratory studies of a single ascending dose of SYNT001 in healthy volunteers. From the NHP studies, single doses of SYNT001 produced a dose-dependent decrease in total IgG and a further decrease was seen with repeated weekly doses up to a maximum 70% reduction at 100 mg/kg. This magnitude of total IgG reduction is approaching the expected maximal effect of 100% inhibition of FcRn function based on murine studies also performed by Syntimmune and others [Roopenian 2003, Nixon 2015]. In the recently completed Phase 1a trial with SYNT001 in healthy volunteers a single dose caused a maximum average 50% drop in total IgG with IV dosing at 30 mg/kg. Based on the NHP studies further reductions are expected following multiple dosing. A comparable decrease in pathogenic autoantibodies is also anticipated.

In the NHP studies, relevant adverse effects, mild-to-moderate infusion reactions, were observed only after the third weekly IV administration, concurrent with the development of anti-SYNT001 antibodies. In the recently completed Phase 1a healthy male volunteer study, the doses of SYNT001 up to and including 30 mg/kg have been well tolerated. There were no dose limiting toxicities, serious adverse events, or any other safety concerns identified. No AEs were observed in the 1 and 3 mg/kg dose cohorts. A single Grade 2 AE was observed; a headache in the 10 mg/kg cohort, treated with acetaminophen. Other subjects had mild (Grade 1) AEs at 10 mg/kg. In Cohort 4 (30 mg/kg), 5 subjects received SYNT001. All five subjects experienced AEs; all were mild (Grade 1), transient and resolved spontaneously without intervention. Therefore, it is anticipated that the doses selected for this study should be well tolerated and have clinically relevant PD effects in patients with chronic pemphigus (vulgaris or foliaceus). For a summary of

findings from the single dose, clinical study in healthy subjects and further details on the nonclinical findings, please refer to the SYNT001 Investigator's Brochure.

2.3 Compliance Statement

This study will be conducted in compliance with Good Clinical Practice (GCP), including the International Conference on Harmonisation (ICH) Guidelines and FDA regulations, consistent with the principles outlined in the Declaration of Helsinki. In addition, the Investigator agrees to adhere to all applicable local laws and regulatory requirements relevant to the use of new therapeutic agents.

The study will be conducted in compliance with the protocol. The appropriate Institutional Review Boards (IRBs) must approve the protocol, any amendments, and the subject informed consent form (ICF) prior to implementation.

Freely given written informed consent must be obtained from every subject prior to participation in this clinical trial. As part of this procedure, the Investigator must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the study subject is aware of the potential risks, inconveniences, or AEs that may occur. The study subject should be informed that he/she is free to withdraw from the study at any time. He/she will receive all information that is required by federal regulations and ICH guidelines. The Investigator or designee will provide the Sponsor with a copy of the IRB-approved informed consent form prior to the start of the study. The rights, safety, and well-being of participating subjects are the most important considerations and should prevail over interests of science and society.

Study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). This trial will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of 5 once-weekly IV infusions of SYNT001 at different dose levels in subjects with chronic pemphigus (vulgaris or foliaceus).

3.2 Secondary Objectives

The secondary objectives of this study are as follow:

- To determine the PK of SYNT001 following 5 once-weekly 1-hour IV infusions at different dose levels
- To assess the effect of 5 once-weekly doses of SYNT001 at different dose levels on the following PD biomarkers:
 - o Immunoglobulins: IgG, IgG subtypes (IgG1-4), IgA, IgM
 - o Albumin
- To assess the effect of 5 once-weekly doses of SYNT001 at different dose levels on the following disease activity markers:
 - o Serum anti-desmoglein (Dsg) (1 and 3) antibody levels
 - o Pemphigus Disease Area Index (PDAI)
- To assess immunogenicity (anti-SYNT001 antibodies)

3.3 Exploratory Objectives

The exploratory objectives of this study are as follow:

- To assess the effect of 5 once-weekly doses of SYNT001 at different dose levels on the following biomarkers, including:
 - o Serum anti-epithelial cell antibody (AECA) levels by indirect immunofluorescence
 - o Circulating immune complexes (CIC)
 - o Complement component 3 (C3)
 - Exploratory biomarkers (FCGR2A single nucleotide polymorphism-SNP, RNAseq, urine IgG)
 - Immune phenotyping by flow cytometry for CD3⁺CD4⁺ T, CD3⁺CD8⁺ T, monocytes, NK cells and B cells
 - o SYNT001 levels in skin biopsies (optional)
- To characterize corticosteroid use during the study

4 STUDY DESIGN

4.1 Study Sites

This study will be conducted at approximately 10 sites in the United States (US).

4.2 Study Endpoints

Primary Outcome Measures: Assessment of safety data (adverse events [AEs], serious adverse events [SAEs], vital sign measurements, ECGs and clinical laboratory tests) will be the primary safety measure.

Secondary Outcome Measures

Pharmacokinetics:

Half-life (t_{1/2}), maximum plasma concentration determined directly from the
concentration-time profile (C_{max}), observed time to reach peak plasma concentration
(T_{max}), area under the plasma concentration-time curve from pre-dose (time 0) to
24 hours post-dose (AUC₀₋₂₄), and area under the plasma concentration-time curve
from pre-dose (time 0) to infinity (AUC_{0-∞})

PD Biomarkers:

- Ig Assessments: Serial assessments of total IgG and IgG subtypes (IgG1-4)
 - o Serial assessments of total IgG and IgG subtypes (IgG1-4)
 - o IgA levels
 - o IgM levels
- Albumin levels

Disease activity markers:

- Serum anti-desmoglein (Dsg) (1 and 3) antibody levels
- Pemphigus Disease Area Index (PDAI) scores

Immunogenicity:

• Anti-SYNT001 antibodies

Exploratory Outcome Measures

Biomarkers, including:

- CIC
- C3
- Serum AECA levels
- Exploratory biomarkers (FCGR2A SNP, RNAseq, urine IgG)

- Immune phenotyping by flow cytometry for measurement of CD3⁺CD4⁺ T, CD3⁺CD8⁺ T, monocytes, NK cells and B cells
- SYNT001 levels in skin biopsies (optional)

Concomitant Treatments

Corticosteroid use

Further details on the statistical and analytical plan for these endpoints are available in Section 12, Statistical Considerations.

4.3 Overview of Study Design

This will be a multicenter, open-label study to assess the safety, tolerability, activity, PK, PD, and immunogenicity of 5 once-weekly IV infusions of SYNT001 to subjects with chronic pemphigus (vulgaris or foliaceus).

Planned doses of SYNT001 to be studied are 10 mg/kg and up to 30 mg/kg. Two cohorts of 8 eligible subjects each will receive 5 once-weekly 60-minute infusions of SYNT001 10 mg/kg or up to 30 mg/kg. Based on review of safety, PD, and clinical outcomes of the first cohort, the dose for the second cohort may be adjusted, but with a maximum dose of 30 mg/kg. Based on review of safety, PD and clinical outcomes from these 2 cohorts, a third cohort of up to 8 subjects may be treated at another dose, with a maximum dose of 45 mg/kg, but may also be lower than 10 mg/kg or between 10 and 30 mg/kg, inclusive.

Cohort	No. of Subjects	Dose
1	8	SYNT001 10 mg/kg
2	8	SYNT001 30 mg/kg

Cohorts will be dosed sequentially beginning with Cohort 1. The first 2 subjects will be dosed at least 24 hours apart. A review of the 24-hour safety data for the first subject will be performed to ensure that there are no overt safety concerns before dosing the second subject. A review of the 7-day safety data for the first 2 subjects will be performed prior to dosing the remaining 6 subjects in the cohort. This evaluation will include a review of AE/SAE reports, vital sign assessments, physical examinations, ECGs and clinical laboratory testing. The seriousness, severity, and relatedness of AEs/SAEs will also be considered in the safety evaluation. Safety data will be reviewed on a continuous basis throughout the study. All data through Day 42

(2 weeks after the last subject's last dose in Cohort 1) will be reviewed before Cohort 2 is initiated. Cohort 2 and Cohort 3, if added, will be dosed per the same schedule.

Safety evaluations will be conducted by a dose escalation committee (DEC). The DEC will consist of the Medical Monitor, an Independent Clinical Expert and a Syntimmune Medical Officer. To assist in the safety assessments, the DEC may request that Investigators, other experts, or members within their organizations review the data and participate in the discussions. Dosing and dose escalation will proceed if the DEC has determined that it would be safe and appropriate to do so. In addition, over the course of the study, the DEC will review any drug-related SAEs to determine if modifications to the study or other measures are necessary to ensure the safety of the subjects.

On days where study drug is administered, vital sign and pulse oximetry measurements will be collected immediately prior to the infusion; 15, 30, and 45 minutes after the start of the infusion; at completion of the infusion; and 30 minutes, 1 hour and 2 hours following completion of the infusion.

On Days 0 and 28, PK blood samples will be collected prior to infusion start and then over the subsequent 48 hours. Subjects will remain at the clinic through the 6-hour PK sample collection and will return to the clinic for the 24- and 48-hour collections. Additional samples will be collected on Days 5 and 33.

On Day 0 photographs will be taken of active lesions. Follow-up photographs will be taken of the same areas on Days 33, 56, 84, and 112. If a subject begins a steroid taper, additional photographs will be taken at the clinic visit during which the decision to begin the taper is made.

Subsequent visits will occur on Days 1, 2, 5, 7, 12, 14, 19, 21, 28, 29, 30, 33, 42 and 56 for safety assessments, study drug dosing, sample collections, and other study procedures.

Subjects also will return to the clinic on Days 84 and 112 for follow-up visits. Subjects whose total IgG is not within 30% of their Day 0 baseline value and not above 500 mg/dL at the Day 112 visit will be referred for further management.

See Table 1 for a schedule of all study events. To assess safety and tolerability, subjects will undergo physical examinations (PEs; including weight), vital sign measurements, clinical (safety) laboratory tests, AE assessments, concomitant medication assessments, and electrocardiograms (ECG).

Note: No vaccinations may be given from within 2 weeks of screening through Day 56. Following Day 56, subjects may receive vaccinations at the discretion of the Investigator.

4.4 Randomization and Blinding

This is an open-label study.

5 STUDY POPULATION

5.1 Target Population

This study will be conducted in approximately 16 male and female subjects (2 cohorts of 8 subjects each) with a confirmed diagnosis of pemphigus (vulgaris or foliaceus); however, a third cohort of up to 8 subjects may be added. Subjects will be enrolled only once in the study and will not be included in subsequent dosing cohorts. Subjects who withdraw for any reason other than an AE and who do not receive study drug or have only received one dose of study drug may be replaced, up to one subject per cohort. Subjects who do not receive all doses of study drug will continue to be followed through all scheduled visits. The maximum number of subjects who may be enrolled in this study is 27 (24 + up to 3 replacements, as necessary). Within each dosing cohort, no more than 3 subjects may be enrolled with pemphigus foliaceus.

5.2 Inclusion Criteria

A subject must meet the following criteria to be eligible for the study:

- 1. Willing and able to read, understand and sign an informed consent form;
- 2. Male or female \geq 18 years of age;
- 3. Documented diagnosis of pemphigus vulgaris or foliaceus based on all 3 of the following criteria:
 - a. Documented clinical history consistent with pemphigus vulgaris or foliaceus (clinical presentation defined as mucosal and/ or skin lesions);
 - b. Presence of Anti-Dsg 1 or 3 antibodies above the upper limit of normal;
 - c. History of at least one positive tissue based test (biopsy, DIF)
- 4. Active disease: Lesions lasting > 2 weeks, and 3 active lesions in skin or mucosa or 2 active lesions with at least one being a skin lesion > 1 cm diameter:
 - a. If treated with rituximab or other anti-CD20 antibodies, last dose > 12 months prior to screening;
 - b. If being treated with other immunosuppressants (i.e., azathioprine, mycophenolate mofetil or cyclosporine), must be on stable dose (< 10% change in dose) for 6 weeks prior to screening;
 - c. If being treated with corticosteroids, must be ≤ 1mg/kg/day and stable (< 10% change in dose) for 2 weeks prior to screening;

- d. Allowed topical therapies for pemphigus lesions upon entering the study include petroleum jelly or Aquaphor® for the skin or chlorhexidine for the mouth
- 5. Body mass index (BMI) $18.5 35.0 \text{ kg/m}^2$;
- 6. Has a negative urine pregnancy test (for women of childbearing potential) documented prior to the first dose of study drug;
- 7. Females of childbearing potential must agree to be abstinent or else use any two of the following medically acceptable forms of contraception (<1% per year failure rate) from the Screening Period through the final study visit: oral contraceptive, condom with or without spermicidal jelly, diaphragm or cervical cap with spermicidal jelly, or intrauterine device (IUD). A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception.
- 8. Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months do not require contraception during the study.
- 9. Males with female partners of childbearing potential, including males who are surgically sterile (post vasectomy), must agree to be abstinent or else use a medically acceptable form of contraception from the screening period through the final study visit.

5.3 Exclusion Criteria

A subject who meets any of the following criteria is ineligible for the study:

- 1. Unable or unwilling to comply with the protocol;
- Active non-hematologic malignancy or history of non-hematologic malignancy in the 3 years prior to screening (exclusive of non-melanoma skin cancer and cervical cancer in situ);
- 3. Positive for HIV or hepatitis C antibody;
- 4. Positive for hepatitis B surface antigen;
- 5. Active infection or history of recurrent infections;
- 6. IVIG treatment within 60 days of screening;
- 7. Received any cytotoxic (other than azathioprine) or mAb therapy in the 3 months prior to screening;

- 8. Any exposure to an investigational drug or device within 30 days prior to screening;
- 9. Plasmapheresis or immunoadsorption within 60 days of screening
- 10. Cellular therapy at any time prior to screening
- 11. Use of any immunosuppressive drugs apart from corticosteroids, azathioprine, mycophenolate mofetil, or cyclosporine within 3 months of screening;
- 12. Serum total IgG < 600 mg/dL;
- 13. Subject has any current medical condition that, in the opinion of the Investigator, may compromise their safety or compliance, preclude successful conduct of the study, or interfere with interpretation of the results (e.g., a significant pre-existing illness or other major comorbidity that the Investigator considers may confound the interpretation of the study results);
- 14. Any vaccination within 2 weeks of screening

6 STUDY PROCEDURES

6.1 Informed Consent

All subjects must take part in the informed consent process. Adequate time must be allowed for the subject to ask questions and make a voluntary decision. No protocol-specific procedures, including screening procedures, are to be performed until the subject has signed and dated an IRB-approved ICF. Subjects may withdraw consent at any time. Participation in the study may be terminated at any time without the subject's consent as determined by the Investigator.

6.2 Demographics and Medical History

Demographics (age, gender, race and ethnicity) and medical history will be obtained from the subject and recorded on the source document and eCRF. Medical history will capture the subject's current medical history (current disease processes), past medical status (past disease processes), history of surgery and concomitant treatments.

6.3 Physical Examination

A complete physical examination will be performed as outlined in Table 1. The complete PE will include measurements of weight (in kg) and height (in cm; height to be measured only at screening visit) and a review of the following body systems:

- General appearance
- Head, eyes, ears, nose, and throat
- Neck
- Respiratory
- Cardiovascular
- Abdomen
- Neurologic
- Extremities
- Dermatologic
- Lymphatic

Any abnormal and clinically significant findings from the PE must be recorded in the appropriate eCRF. Findings at screening and Day 0 (pre-dose) will be recorded as medical history.

6.4 Pemphigus Disease Area Index (PDAI) Scoring

Pemphigus severity and disease activity will be measured using the PDAI. See Appendix B.

6.5 Vital Sign Measurements

Vital sign measurements will be collected after the subject has been sitting for 5 minutes. Vital sign assessments will include measurements of sitting blood pressure (mm Hg), heart rate (beats

per minute), respiration rate (breaths per minute), oral temperature (Celsius). Abnormal results are to be repeated after 5 minutes of rest. Pulse oximetry (%) also is to be measured. See Table 2 for timing window allowances with respect to measurement collection.

On Days 0, 7, 14, 21, and 28, vital sign measurements are to be obtained immediately prior to the infusion; 15, 30, and 45 minutes after the start of the infusion; at completion of the infusion; and 30 minutes, 1 hour and 2 hours following completion of the infusion. Details on the management of mild to moderate and severe infusion reactions can be found in Figure 1 and Figure 2. Abnormalities in vital sign measurements will be graded in severity per the NCI CTCAE scale Version 4.03.

Subjects should be seated quietly for at least 5 minutes in a chair with their backs supported, their feet flat on floor (legs uncrossed), and their arms bared on a hard surface, with the arm slightly abducted and bent, with palm up and the midpoint of upper arm at heart level. Correct cuff and bladder size should be utilized and the same cuff and arm should be used per subject throughout study.

6.6 12-Lead Electrocardiogram (ECG)

Digital 12-lead ECG measurements will be obtained at screening, on Days 0 and 28 at 5 minutes after the completion of the infusion and at the Day 56 visit. Subjects who conduct their Day 12 visit at the investigative site, as opposed to an at-home nurse visit, will have an additional ECG performed. ECGs are to be performed with the subject in a supine position having rested in this position for at least 5 minutes before each reading. ECGs are to be performed in triplicate, each 1 to 2 minutes apart. See Table 2 for timing window allowances with respect to performing ECG.

The following ECG parameters will be collected: PR interval, RR interval, QRS interval, and QT interval. The ECG findings will be evaluated by a qualified physician for the presence of abnormalities (qualitative assessment). The physician will assess each ECG as normal, abnormal/not clinically significant, or abnormal/clinically significant.

Normal QTcF is ≤ 450 msec.

Abnormalities in the ECG that appear following therapy or that result in clinical signs and symptoms are considered clinically significant for the purposes of this study and will be recorded on the AE eCRF.

6.7 Clinical Laboratory Measurements

Collection time for all safety, PD, and exploratory labs are outlined in Table 1.

Laboratory testing (hematology, urinalysis, serum chemistry, virology, serology, pregnancy tests, PD samples, PK samples, and anti-drug antibody samples) will be performed using established methods by a central laboratory. Safety laboratory panels are defined as listed in Table 3. Blood and urine samples for hematology, serum chemistry, and urinalysis will be prepared using standard procedures. Results will be provided to the Investigator. Aliquots from the PK, biomarker and anti-drug antibody samples may be retained as back-up for additional testing as necessary. Subjects will be in a seated or supine position during blood collection. Full clinical safety lab draws will be collected at Screening and on Days 0, 7, 14, 21, 28, 33, 42, 56, 84 and 112. The total blood draw for each subject who completes the study at Day 112, will be approximately 381 mL. Please refer to the Laboratory Manual for more information.

Table 3: Clinical Laboratory Panels

Hematology	Serum Chemistry	Urinalysis
CBC with differential and blood smear Erythrocyte Sedimentation Rate (ESR)	 Albumin Alkaline phosphatase ALT AST BUN Calcium Carbon dioxide Chloride Creatinine Glucose LDH Phosphorus Potassium Sodium Total and direct bilirubin Total protein Uric acid C-Reactive Protein 	 Appearance Color pH Specific gravity Ketones Protein Glucose Nitrite Urobilinogen Blood/hemoglobin Leukocyte esterase Bilirubin Microscopic examination of sediment: only if the results of the urinalysis dipstick evaluation are positive for blood/hemoglobin
Virology		
Hepatitis CHepatitis B		

- HIV
- VZV
- Tetanus

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count; BUN = blood urea nitrogen; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; VZV = varicella-zoster virus

Abnormalities in clinical laboratory tests that are considered clinically significant are to be recorded on the AE electronic case report form (eCRF) page. Laboratory results will be graded using the NCI CTCAE, Version 4.03. If laboratory values constitute part of an event that meets criteria defining it as serious, the event (and associated laboratory values) must be reported as an SAE (see Section 11.3.1).

6.7.1 Pregnancy Testing

Pregnancy testing will be performed for women of childbearing potential at screening and prior to first dose of SYNT001 on Day 0 and Days 56 and 112 (urine or serum test is acceptable however, positive urine tests must be confirmed with serum testing.)

6.7.2 Virology

Testing for HCV antibody, hepatitis B surface antigen, and HIV antibody will be performed at screening.

6.7.3 Serum Tetanus Antibody and Varicella-Zoster Virus Antibody Testing

Samples for serum tetanus antibody and varicella-zoster virus antibody testing are to be collected at baseline (pre-dose, Day 0) and on Day 56 (Follow-Up visit). Testing at Day 56 will not be done for any subject whose baseline titer is below the level of detection. Specifically, if the baseline VZV titer is above the detectable level, but tetanus is not, only the VZV antibody titer will be tested on Day 56. If the Day 56 results are below the baseline value, defined as greater than 30% below the baseline value, or if the subject falls below the level of detection, the subject will be re-tested at Day 84; if still below the baseline value (or level of detection), the subject will be re-tested at Day 112. Any subject whose baseline value for tetanus or VZV was above the detectable level at baseline, and is not within 30% of the baseline value or is below the detectable level by Day 112, will be referred to their primary care physician for further management.

6.7.4 Pharmacokinetics (PK) Sampling

Starting on Days 0 and 28, serum samples will be collected just prior to the start of study drug infusion (pre-dose), at 5 minutes and 2, 4, 6, 24, and 48 hours after the end-of-study drug

infusion. Additional samples will be collected on Days 5 and 33. The actual time and date of each blood draw is to be recorded.

Study drug concentration will be used to calculate the following PK parameters: $t_{1/2}$, C_{max} , T_{max} , AUC_{0-24} , and $AUC_{0-\infty}$.

Detailed instructions for sample collection and preparation will be provided in a separate laboratory manual

6.7.5 Pharmacodynamic Sampling

PD samples will be collected for analyses throughout the study. On Days 0, 7, 14, 21, and 28, samples should be collected prior to infusion of study drug. Measurements for albumin PD biomarkers will be derived from the clinical safety laboratory results. Samples for each type of PD will be collected according to the schedule shown in **Table 4**.

Table 4: Pharmacodynamic/ Activity Assessments

Parameter	Collection Timepoints	
IgG, IgG subtypes (IgG1-4), IgA, IgM	Screening, and Days 0, 1, 2, 5, 7, 12, 14, 19, 21, 28, 29, 30, 33, 42, 56, 84 and 112.	
Circulating immune complexes (CIC)	Days 0, 5, 7, 12, 14, 19, 21, 28, 33, 42, 56, 84 and 112	
• Albumin	Screening, and Days 0, 7, 14, 21, 28, 33, 42, 56, 84 and 112	
Anti-Dsg (1 and 3) antibody titer	Screening, Days 0, 7, 14, 33, 56, 84 and 112	
 Complement component 3 (C3) Anti-epithelial cell antibody (AECA) levels by indirect immunofluorescence 	Days 0, 14, 33, 56, 84 and 112	
Exploratory biomarker (RNAseq, Urine IgG)	Days 0, 14, 33, 56, 84 and 112	
Immune phenotyping by flow cytometry for measurement of CD3 ⁺ CD4 ⁺ T, CD3 ⁺ CD8 ⁺ T, monocytes, NK cells and B cells	Days 0, 28 and 56	
Exploratory biomarker (FCGR2A SNP)	Day 0	

See Table 2 for timing window allowances with respect to measurement collection. Detailed instructions for sample collection (including collection tubes) and preparation will be provided in a separate laboratory manual.

6.7.6 Immunogenicity Testing

Serum samples will be collected for immunogenicity analyses on Days 0 (pre-dose), 14, 28, 56, 84 and 112.

SYNT001 is being developed for the acute and chronic therapy of autoimmune disorders. Although SYNT001 is a humanized IgG4 monoclonal antibody, exposure to SYNT001 in clinical trials could result in the development of anti-drug antibodies (ADAs), with potential consequences ranging from neutralization or lessening of drug efficacy to safety consequences such as allergic reactions. Testing will first detect binding ADAs, then, for all confirmed positive samples, there will be testing for neutralizing effects.

Detailed instructions for sample collection and preparation will be provided in a separate laboratory manual.

6.8 **Study Drug Administration**

Two cohorts of 8 eligible subjects each will receive 5 once-weekly 60-minute IV infusions of SYNT001 10 mg/kg or up to 30 mg/kg. SYNT001 will be given as a 250-mL IV infusion over 1 hour using a 0.2-micron, inline filter. Based on review of safety data, as well as available and relevant PD results, and clinical outcomes of Cohort 1, a decision about proceeding with Cohort 2 will be made. Based on review of all safety data, available PD results, and clinical outcomes of these 2 cohorts, a third cohort of 8 subjects may be treated at another dose, with a maximum dose of 45 mg/kg, but may also be lower than 10 mg/kg or between 10 and 30 mg/kg, inclusive.

Cohort No.	Study Drug	Dose Level (mg/kg/dose)
1	SYNT001	10 mg/kg
2	SYNT001	30 mg/kg

See Section 9.1 for dosing schedule.

6.9 **Prior and Concomitant Medications**

All medications a subject receives within 14 days prior to enrollment through the end of the study will be documented on the source document and eCRF.

Note: No vaccinations may be given from within 2 weeks of screening through Day 56. Following Day 56, subjects may receive vaccinations at the discretion of the Investigator.

6.10 **Adverse Event Assessments**

Information regarding the occurrence of AEs will be collected from the time the subject signs the informed consent form and continuing through the last study visit. Findings at screening and Day 0 (pre-dose) will be recorded as medical history. Any known untoward event that occurs beyond the AE reporting period that the Investigator assesses as related to study drug also should be reported as an AE.

Clinical AEs will be graded using the NCI CTCAE, Version 4.03 (Appendix A).

Note: AEs resulting in a subject's permanent discontinuation from the study, regardless of seriousness or relationship to study drug, MUST be promptly reported to the sponsor. Additionally, subjects must be followed until return to normal and/or resolution of the AE.

See Section 11 for more information.

6.11 Photographs

On Day 0 photographs will be taken of active lesions. Follow-up photographs will be taken of the same areas on Days 33, 56, 84 and 112. Subjects who begin a steroid taper will have additional photographs taken at the clinic visit during which the decision to begin the taper is made. A separate manual describing the procedures for taking photographs will be provided.

6.12 Skin Biopsy

Optional skin biopsy samples will be collected on Day 0 pre-dose and on Days 1, 2, 14, 33, 56 and 84 to analyze SYNT001 levels.

7 STUDY ASSESSMENTS

7.1 Screening Period: Day -14 to Day -1

Informed consent must be obtained before any study-specific samples are taken or study-specific tests or evaluations are conducted. The following assessments at the screening visit are to occur within 14 days before dosing. Study eligibility will be based on satisfying all the study inclusion and exclusion criteria.

At the screening visit, information will be collected and subjects will have clinical evaluations as follows:

- Informed consent (Section 6.1)
- Medical history and demographic data (Section 6.2)
- Review inclusion and exclusion criteria (Section 5.2, Section 5.3)
- Complete PE, including height and weight (Section 6.3)
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- 12-Lead ECG (to be obtained in triplicate after 5 minutes of rest in the supine position) (Section 6.6)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section
- Pregnancy test (Section 6.7)
- Hepatitis and HIV screen (Section 6.7)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - Anti-Dsg (1 and 3) antibody titer
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.2 **Enrollment and First Treatment: Day 0**

Study Day 0 is defined as the date the subject is administered their first dose of study drug. On Day 0, subjects will be asked to come to the clinic and the following procedures will be performed prior to the first dose of study drug:

- Complete physical exam (Section 6.3)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature); to be measured immediately prior to the infusion (Section 6.5)
- Pulse oximetry (to be measured immediately prior to the infusion) (Section 6.5)

- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- Pregnancy test (Section 6.7)
- Serum tetanus antibody and VZV antibody (Section 6.7)
- PDAI Score (Section 6.4)
- PK baseline sample collection (collected just prior to the start of the study drug infusion) (Section 6.7)
- Immunogenicity sample collection (collected just prior to the start of study drug infusion) (Section 6.7)
- PD sample collection (collected just prior to the start of the study drug infusion) (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - Anti-Dsg (1 and 3) antibody titer
 - CIC
 - C3
 - AECA
 - FCGR2A SNP
 - RNAseq
 - Urine IgG
 - Immune phenotyping
- Optional skin biopsy (Section 6.12)
- Photography (Section 6.11)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After the preceding procedures and assessments are completed:

- Study drug administration (record date and time of dose of study drug) (Section 9)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) will be performed at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion (Section 6.5)
- Pulse oximetry will be measured at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion (Section 6.5)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After administration of study drug, the following post treatment procedures and assessments will be performed:

• Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral

temperature): 30 minutes, 1 hour and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest (Section 6.5)

- Pulse oximetry: 30 minutes, 1 hour and 2 hours following completion of the infusion (Section 6.5)
- PK sample collection at 5 minutes and 2, 4, 6 hours after the end-of-study drug infusion; record collection date and time for each PK sample (Section 6.7)
- 12-Lead ECG (to be obtained in triplicate at 5 minutes after the completion of study drug infusion (Section 6.6)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.3 Follow-up: Day 1

On Day 1 (24 hours \pm 1 hour from end-of-infusion time on Day 0), the subject will return to the clinic and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
- PK sampling (record collection date and time) (Section 6.7)
- Optional skin biopsy (Section 6.12)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.4 Follow-up: Day 2

On Day 2 (48 hours \pm 2 hours from end-of-infusion time on Day 0), the subject will return to the clinic and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
- PK sampling (record collection date and time) (Section 6.7)
- Optional skin biopsy (Section 6.12)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.5 Follow-up: Day 5

On Day 5 (120 hours \pm 4 hours from end-of-infusion time on Day 0), subjects may return to the clinic or be visited by at-home nurse, and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- PK sampling (record collection date and time) (Section 6.7)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.6 Treatment Day 7 (Dose 2)

On Day 7 (\pm 6 hours) subjects will return to the clinic and the following procedures are to be performed prior to study drug infusion:

- Complete physical exam (Section 6.3)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature); to be measured immediately prior to the infusion (Section 6.5)
- Pulse oximetry (to be measured immediately prior to the infusion) (Section 6.5)
- PDAI Score (Section 6.4)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- PD sample collection (collected just prior to the start of the study drug infusion) (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titer
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After the preceding procedures and assessments are completed:

- Study drug administration (record date and time of dose of study drug) (Section 9)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) will be performed at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion (Section 6.5)
- Pulse oximetry will be measured at 15, 30, and 45 minutes after the start of the infusion

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and at completion of the infusion (Section 6.5)

- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After administration of study drug, the following post treatment procedures and assessments will be performed:

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature): 30 minutes, 1 hour and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Pulse oximetry: 30 minutes, 1 hour and 2 hours following completion of the infusion (Section 6.5)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.7 Dose 2 Follow-up Day 12

On Day 12 (\pm 6 hours) the subject may return to the clinic, or be visited by at-home nurse, and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
- If visit performed at the study site: 12-Lead ECG to be obtained in triplicate (Section 6.6)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.8 Treatment Day 14 (Dose 3)

On Day 14 (\pm 6 hours) subjects will return to the clinic and the following procedures are to be performed prior to study drug infusion:

- Complete physical exam (Section 6.3)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature); to be measured immediately prior to the infusion (Section 6.5)
- Pulse oximetry (to be measured immediately prior to the infusion) (Section 6.5)
- PDAI Score (Section 6.4)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)

- Immunogenicity sample collection (collected just prior to the start of study drug infusion) (Section 6.7)
- PD sample collection (collected just prior to the start of the study drug infusion) (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - Anti-Dsg (1 and 3) antibody titer
 - CIC
 - C3
 - AECA
 - RNAseq
 - Urine IgG
- Optional skin biopsy (Section 6.12)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After the preceding procedures and assessments are completed:

- Study drug administration (record date and time of dose of study drug) (Section 9)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) will be performed at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion (Section 6.5)
- Pulse oximetry will be measured at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion (Section 6.5)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After administration of study drug, the following post treatment procedures and assessments will be performed:

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature): 30 minutes, 1 hour and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Pulse oximetry: 30 minutes, 1 hour and 2 hours following completion of the infusion (Section 6.5)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.9 Dose 3 Follow-up Day 19

On Day 19 (± 6 hours) the subject may return to the clinic, or be visited by an at-home nurse, and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.10 **Treatment Day 21 (Dose 4)**

On Day 21, $(\pm 6 \text{ hours})$ subjects will return to the clinic and the following procedures are to be performed prior to study drug infusion:

- Complete physical exam (Section 6.3)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature); to be measured immediately prior to the infusion (Section 6.5)
- Pulse oximetry (to be measured immediately prior to the infusion) (Section 6.5)
- PDAI Score (Section 6.4)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section
- PD sample collection (collected just prior to the start of the study drug infusion) (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After the preceding procedures and assessments are completed:

- Study drug administration (record date and time of dose of study drug) (Section 9)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) will be performed at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion (Section 6.5)
- Pulse oximetry will be measured at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion (Section 6.5)
- Concomitant medication assessment (Section 6.9)

• AE assessment (Section 6.10)

After administration of study drug, the following post treatment procedures and assessments will be performed:

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature): 30 minutes, 1 hour and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Pulse oximetry: 30 minutes, 1 hour and 2 hours following completion of the infusion (Section 6.5)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.11 Treatment Day 28 (Dose 5)

On Day 28 (\pm 6 hours), subjects will return to the clinic and the following procedures are to be performed prior to study drug infusion:

- Complete physical exam (Section 6.3)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature); to be measured immediately prior to the infusion (Section 6.5)
- Pulse oximetry (to be measured immediately prior to the infusion) (Section 6.5)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- PDAI Score (Section 6.4)
- PK sampling (collected just prior to the start of the study drug infusion; record collection date and time for each PK sample) (Section 6.7)
- Immunogenicity sample collection (collected just prior to the start of study drug infusion) (Section 6.7)
- PD sample collection (collected just prior to the start of the study drug infusion) (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Immune phenotyping
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After the preceding procedures and assessments are completed:

- Study drug administration (record date and time of dose of study drug) (Section 9)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) will be performed at 15, 30, and 45 minutes after the start of the infusion

- and at completion of the infusion (Section 6.5)
- Pulse oximetry will be measured at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion (Section 6.5)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After administration of study drug, the following post treatment procedures and assessments will be performed:

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature): 30 minutes, 1 hour and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Pulse oximetry: 30 minutes, 1 hour and 2 hours following completion of the infusion (Section 6.5)
- PK sample collection at 5 minutes and 2, 4, 6 hours after the end-of-study drug infusion; record collection date and time for each PK sample (Section 6.7)
- 12-Lead ECG (to be obtained in triplicate at 5 minutes after the completion of study drug infusion (Section 6.6)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.12 Follow-up Day 29

On Day 29 (24 hours \pm 1 hour from end-of-infusion time on Day 28), the subject will return to the clinic and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
- PK sampling (record collection date and time) (Section 6.7)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.13 Follow-up Day 30

On Day 30 (48 hours \pm 2 hours from end-of-infusion time on Day 28), the subject will return to the clinic and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
- PK sampling (record collection date and time) (Section 6.7)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.14 Follow-up Day 33

On Day 33 (120 hours \pm 4 hours from end-of-infusion time on Day 28), subjects will return to the clinic and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- PDAI Score (Section 6.4)
- PK sampling (record collection date and time) (Section 6.7)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titer
 - C3
 - AECA
 - RNAseq
 - Urine IgG
- Optional skin biopsy (Section 6.12)
- Photography (Section 6.11)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

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7.15 Follow-up Day 42

On Day 42 (\pm 3 days), subjects will return to the clinic and the following procedures are to be performed:

- Complete physical exam (Section 6.3)
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section
- PDAI Score (Section 6.4)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.16 Follow-up Day 56

On Day 56 (\pm 5 days), subjects are to return to the clinic and the following procedures are to be performed:

- Complete physical exam (Section 6.3)
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section
- Pregnancy test (Section 6.7)
- 12-Lead ECG (to be obtained in triplicate after 5 minutes of rest in the sitting position) (Section 6.6)
- Serum tetanus antibody and VZV antibody; Testing at Day 56 will not be done for any subject whose baseline titer is below the level of detection. See Section 6.7.3 for additional information.
- Immunogenicity sample collection (Section 6.7)
- PDAI Score (Section 6.4)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titer

- C3
- AECA
- RNAseq
- Urine IgG
- Immune phenotyping
- Optional skin biopsy (Section 6.12)
- Photography (Section 6.11)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.17 Follow-up Day 84

On Day 84 (\pm 5 days), subjects are to return to the clinic and the following procedures are to be performed:

- Complete physical exam (Section 6.3)
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- Serum tetanus antibody and VZV antibody testing if required. See Section 6.7.3 for additional information.
- Immunogenicity sample collection (Section 6.7)
- PDAI Score (Section 6.4)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titer
 - C3
 - AECA
 - RNAseq
 - Urine IgG
- Optional skin biopsy (Section 6.12)
- Photography (Section 6.11)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

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7.18 Follow-up Day 112 (End-of-Study) or Early Termination Visit

On Day 112 (\pm 5 days), subjects are to return to the clinic and the following procedures are to be performed:

- Complete physical exam (Section 6.3)
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- Pregnancy test (Section 6.7)
- Serum tetanus antibody and VZV antibody testing if required. See Section 6.7.3 for additional information.
- Immunogenicity sample collection (Section 6.7)
- PDAI Score (Section 6.4)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titer
 - C3
 - AECA
 - RNAseq
 - Urine IgG
- Photography (Section 6.11)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

8 REMOVING SUBJECTS FROM STUDY

Every reasonable effort will be made to keep the subject in the study; however, if a subject is withdrawn from the study, every effort will be made by the Investigator to complete and report the reasons for withdrawal as thoroughly as possible. The reason(s) for termination must be clearly documented on the appropriate page of the eCRF. Once a subject discontinues from the study for any reason, every effort will be made to collect all clinical and laboratory data as scheduled for the Early Termination Visit (See Table 1). A termination eCRF must be completed for all enrolled subjects.

8.1 Subject Withdrawal

A subject's participation in the study may be prematurely discontinued for any of the following reasons:

- 1. The subject wishes to withdraw from the study.
- 2. Request by a regulatory agency (e.g., Institutional Review Board).
- 3. Subject experiences a significant or intolerable AE.
- 4. The subject experiences a significant adverse change in vital signs, PE findings, or a clinical laboratory parameter.
- 5. The subject has a need for a concomitant medication that is not permitted by the study protocol.
- 6. The subject experiences generalized impairment or mental incompetence that would result in the subject being unable to understand his or her participation in the study.
- 7. If, in the Investigator's medical judgment, further participation would be injurious to the health and well-being of the subject, or is not in the best interest of the subject.
- 8. Administrative reasons, such as subject non-compliance or a major protocol violation.

Subjects who are withdrawn from this study due to an AE determined to be related to study drug are to be followed until there is either:

- Resolution or stabilization of the AE determined to be related
- The subject is lost to follow-up
- The event is otherwise explained

If there is a persistent AE contributing to discontinuation that is determined to be related to SYNT001, subjects must be followed with appropriate medical management until resolution or stabilization.

A reasonable effort should be made to contact any subject lost to follow-up during the study to complete assessments and retrieve any outstanding data. If the subjects are unreachable by telephone after three (3) attempts, the minimum of a registered letter should be sent requesting that contact be made with the Investigator to report survival information.

8.2 Study Discontinuation

Syntimmune Inc. has the right to terminate or to stop the study at any time. Reasons for study discontinuation may include, but are not limited to the following:

- The incidence or severity of AEs in this or other related studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory
- Drug supply issues
- Excessive subject self-withdrawal
- Significant protocol violations (e.g., violation of eligibility criteria, dosing errors, missing data for study endpoint analysis)

8.3 Replacements

Enrolled subjects withdrawn for a reason other than an AE will be replaced if they have not been dosed or have only received one dose of study drug at the time of discontinuation, up to one subject per cohort. Subjects who do not receive all doses of study drug will continue to be followed through all scheduled study visits.

8.4 Stopping Rule

8.4.1 Dose-Escalation Stopping Rule

Dose escalation decisions will be made by a Dose Escalation Committee (DEC) and will be based on safety and pharmacodynamic evaluations including but not limited to, dose-limiting toxicities, AEs, SAEs, and total IgG levels.

Dose-limiting toxicity (DLT) will be defined generally as severe (Grade 3) AEs occurring in \geq 2 subjects that are determined to be clinically significant and considered related to study drug.

If 2 or more subjects at any time in any cohort (8 total subjects per cohort) have Grade 3 AEs that are determined to be clinically significant and considered to be related to study drug, dosing will be halted within that cohort and dose-escalation to a higher dose will not occur. If the dose-escalation stopping rule is met during Cohort 1 (10 mg/kg) all safety data and all available pharmacodynamics will be reviewed and the cohort may resume (if applicable) or a new cohort may be added at a dose at least 50% lower than the 10 mg/kg dose. If the stopping rule is not met in Cohort 1, dose-escalation may proceed up to a maximum of 30 mg/kg. If the dose-escalation stopping rule is met for the first time during Cohort 2, all safety data and all available pharmacodynamics will be reviewed and the cohort may resume (if applicable) or a new cohort may be added at a dose a minimum of 30% lower than the Cohort 2 dose. If the stopping rule is not met in Cohort 2, dose-escalation may proceed up to a maximum of 45 mg/kg; however, this cohort may also receive a dose equal to or less than 30 mg/kg based on evaluation of all safety and pharmacodynamic data.

8.4.2 Study Stopping Rule

If any subject experiences a life-threatening AE (Grade 4) that is considered to be related to study drug, further dosing in all enrolled subjects will be suspended until the DEC has evaluated the event and determined the appropriate course of action. At any time during the study, the study may be discontinued if the DEC determines that further drug exposure would pose an undue risk to subjects.

8.4.3 Individual Stopping Rule

Dosing for any individual subject will be discontinued (i.e., no further study drug will be given to that subject) if the subject experiences any study drug-related SAE or any study drug-related non-SAE adverse event that, in the judgement of the Investigator (following consultation with the Medical Monitor, if desired) suggest that it could be unsafe to administer further study drug to that subject. Additionally, a subject will be discontinued from further treatment with study drug, at the discretion of the Investigator with consultation with the Medical Monitor, if they require a significant increase in dose(s) of anti-pemphigus medication(s) for the management of pemphigus.

9 STUDY DRUG

For detailed information regarding SYNT001 preparation and administration, refer to the Pharmacy Manual.

9.1 SYNT001

SYNT001 is provided in vials containing 5 mL SYNT001 (extractable volume) at a nominal concentration of 50 mg/mL. The product is supplied as a liquid at pH 6.5 ± 0.5 . SYNT001 is diluted in Dextrose 5% in Water (D5W) to prepare the solution for infusion. SYNT001 will be infused via IV in 250 mL over 1 hour using a 0.2-micron, inline filter.

Two cohorts of 8 eligible subjects each will receive 5 once-weekly 60-minute infusions of SYNT001 in planned doses of 10 mg/kg or 30 mg/kg. Based on review of safety, PD, and clinical outcomes of these two cohorts, a third cohort of up to 8 subjects may be treated at another dose, with a maximum dose of 45 mg/kg, but may also be lower than 10 mg/kg or between 10 and 30 mg/kg, inclusive.

The specification for host cell DNA in SYNT001 is < 2 pg/mg, the limit of quantitation of the assay. To comply with regulatory guidelines, which specify a maximum level of 10 ng host cell DNA per dose, dosing is limited to 5000 mg of SYNT001. Therefore, at the highest dose possible in this study (45 mg/kg), maximum subject weight will be limited to 111 kg.

9.2 Cohort Dosing

Cohorts will be dosed sequentially beginning with Cohort 1. The first 2 subjects will be dosed at least 24 hours apart. A review of the 24-hour safety data for the first subject will be performed to ensure that there are no overt safety concerns before dosing the second subject. A review of the 7-day safety data for the first 2 subjects will be performed prior to dosing the remaining 6 subjects in the cohort. Cohort 2, and Cohort 3 if added, will be dosed per the same schedule

9.3 Timing of Dosing

On Days 0, 7, 14, 21, and 28, subjects will receive a 60-minute IV infusion of SYNT001 in the morning. The date and time the dose is administered will be recorded.

9.4 Identity of Investigational Products

All supplies of SYNT001 will be supplied by Syntimmune and must be stored refrigerated (2°C to 8°C/36°F to 46°F) in the carton and protected from light, in a securely locked area, accessible to authorized persons only, until needed for dose preparation. Qualified site personnel will

inventory the investigational product received and will maintain records of disposition of the drug, including dates, quantity and use.

9.5 **Investigational Product Retention at Study Site**

The Investigator (or designee) is responsible for maintaining accurate accountability records of the investigational product throughout the clinical study. All study drug received at the site must be inventoried and accounted for in an accountability log provided by the Sponsor. All dispensing and accountability records will be available for Sponsor review. Study drug accountability will be verified during on-site monitoring visits.

Upon the completion or termination of the study, and upon written authorization from the Sponsor, or its representative, all unused and/or partially used study drug should be returned or destroyed at the investigational site, as specified by Sponsor. It is the Investigator's responsibility to ensure that the Sponsor, or its representative, has provided written authorization that procedures for proper disposal of the study drug have been established, and that appropriate records of the disposal are documented and maintained. No unused study drug may be disposed until fully accounted for by the Sponsor monitor (or designee)

9.6 **Warnings and Precautions**

Note: Subjects must not receive any vaccinations from within 2 weeks of screening until Day 56.

9.6.1 **Infusion Reaction**

SYNT001 will be given as an IV infusion over 1 hour. As with all mAbs administered by IV infusion, infusion reactions are possible. In nonclinical testing of SYNT001 in NHPs, clinical observations were limited to infusion reactions due to the immunogenicity of SYNT001 in NHPs. These reactions included transient emesis/vomitus which typically occurred within 1 hour of dosing at all dose groups, but only after the third weekly infusion following the development of ADAs. Transient histamine-type responses were noted 30 minutes post-dose in some animals in all dose groups, but only following the third weekly infusion as above. These reactions were consistent with a histamine reaction (decreased activity, periocular swelling, erythema, facial flushing, eyelids partially/completely closed, and/or generalized weakness). With the exception of vomitus/emesis and red skin discoloration associated with injection or blood draw sites, these observations spontaneously resolved within 1-hour post-dose. Subsequent pretreatment with intramuscular diphenhydramine prevented further histamine-type reactions. All doses of SYNT001 were administered by bolus infusion over approximately 5 minutes in the NHP studies. However, all of the observed infusion reactions (including vomitus/emesis and

histamine-type reactions) associated with ADAs are not at all predictive of what may occur in humans [Bugelski 2004, Ponce 2009] and furthermore, are not considered relevant to predicting responses in humans [ICH S6(R1) 2011].

Typically, infusion reactions to monoclonal antibodies observed in human studies develop within 30 minutes to 2 hours after the initiation of drug infusion, although symptoms may be delayed for up to 24 hours. Most are mild in severity, although severe and even fatal reactions can occur.

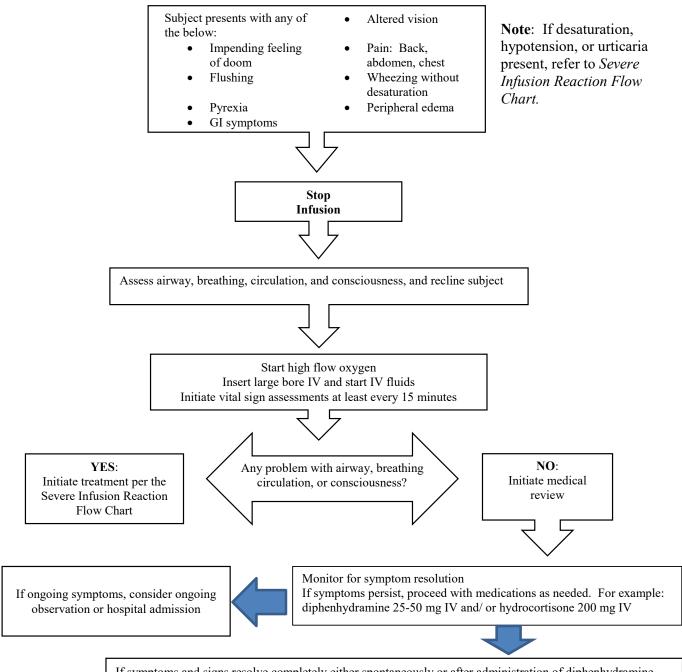
Guidelines for Grading and Management of Allergic or Infusion-Related Reactions

Allergic and/or infusion-related reactions include hypersensitivity reactions and cytokine release syndromes. These reactions are experienced by patients during or within hours of the infusion of monoclonal antibody therapy. Symptoms can include flushing, alterations in heart rate and blood pressure, dyspnea, bronchospasm, back pain, fever, urticaria, edema, nausea, and all types of rashes. Anaphylaxis is recognized as a severe, life-threatening, generalized, or systemic reaction. This is a medical emergency characterized by rapidly developing life-threatening airway and/or breathing and/or circulation problems usually associated with skin or mucosal changes.

Management of Grade 1 infusion reactions include decreasing the rate of infusion by 50% and observing. Symptoms may also be treated as needed with medications such as diphenhydramine, hydrocortisone or acetaminophen.

Management of Grade 2 and higher infusion reactions should include stopping the infusion of study drug. See Figure 1 and Figure 2 for details on the management of Grades 1-2 and Grade 3 or higher infusion reactions. The severity of and management of allergic or infusion-related reactions will be graded and managed using NCI CTCAE Version 4.03 (see Table 5).

Figure 1: Management of Mild (Grade 1) to Moderate (Grade 2) Infusion Reactions



If symptoms and signs resolve completely either spontaneously or after administration of diphenhydramine with or without hydrocortisone, consider rechallenge:

Wait at least 20 minutes following medication administration before commencing rechallenge at an infusion rate of 50% or less of the initial infusion rate or

Consider pre-medicating the subject with the same medication(s) 20-30 minutes in advance of subsequent administrations of SYNT001 and starting infusion at 50% of the planned infusion rate for the first 30 minutes, then returning to the intended infusion rate in the absence of any infusion reaction

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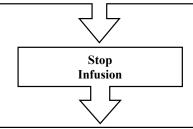
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Figure 2: Management of Severe (Grade 3 or higher) Infusion Reactions

Subject presents with any of the below:

- Urticaria
- Airway threatened by angioedema
- Angioedema: Lip, mouth, facial swelling
- Respiratory compromise wheezing, dyspnea, stridor or hypoxia
 (O2 saturation < 90%)
- BP < 90 mmHg SBP or >30% decrease from patient baseline



Start basic life support:

- High oxygen flow
- On bed, head down, legs up
- Large bore IV cannula, 1 L normal saline STAT
- Initiate vital signs at least every 15 minutes



Consider (under medial direction):

Epinephrine 1:1000

• 0.3 mg (0.3 mL) IM into lateral thigh



Airway Threatened: Nebulized epinephrine 1:1000, 3–5 mL (3–5 mg)

Bronchospasm: Nebulized salbutamol 5 mg

(Wheeze or Hypoxia) Consider: Intubation / nebulized epinephrine

Hypotension: Place on cardiac monitor

(Systolic BP <100 mmHg) Further epinephrine 1:1000, 0.3 mg IM and

IV normal saline bolus 20 mL/kg STAT as needed

Have vasopressin on hand



Transfer to Emergency Room/ICU Observe until all symptoms resolved.

Table 5: Grading and Management of Allergic or Infusion-Related Reactions

Adverse Event	Grade				
	1	2	3	4	5
Infusion- Related Reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids): prophylactic medications indicated for ≤ 24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement, hospitalization indicated for clinical sequelae	Life- threatening consequences; urgent intervention required	Death
Allergic Reaction	Transient flushing or rash, drug fever < 38.0°C. Intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids): prophylactic medications indicated for ≤ 24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement, hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life- threatening consequences; urgent intervention required	Death
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticarial; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life- threatening consequences; urgent intervention required	Death
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids): prophylactic medications indicated for ≤ 24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement, hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life- threatening consequences; pressor or ventilator support indicated	Death

Abstracted from NCI CTCAE Version 4.03.

9.6.2 Potential Immune Effects

An antibody blocking FcRn is anticipated to have several effects. These include acceleration of catabolism of IgG, but not other immunoglobulin isotypes such as IgA and IgM, leading to dose-dependent decreases in circulating IgG levels by up to an estimated 50% from the baseline levels after a single dose and further decreases after multiple doses up to a 70% to 80% reduction. Based on studies in humans, it is expected that with a single dose, the nadir of this effect will occur approximately 5 days after dosing. The time course of recovery of IgG following dosing in the Phase 1a study suggests that a return to within 30% of baseline levels observed at pretreatment occurs within 4 weeks after a single dose and within 4 weeks after multiple doses as shown in NHPs.

Given the normal adult range of IgG of 500 to 1600 mg/dL (Agarwal and Cunningham-Rundles, 2007; Furst, 2009; Gonzalez-Quintela et al, 2008; Joliff et al, 1982; Keystone et al, 2007; McMillan et al, 1997; van Vollenhoven et al, 2013), with a mean of 1150 mg/dL, a 50% decrease in the mean would be to 575 mg/dL and a 50% decrease from the low end of the normal range used for the inclusion criteria of 600 mg/dL would be to 300 mg/dL. An 80% decrease from baseline after multiple doses would result in IgG levels of 230 mg/dL and 120 mg/dL, respectively. While these levels are in the range found in patients with primary humoral immunodeficiency [Ameratunga 2013], the levels will be transient. Further, as reported for other therapies used for pemphigus, the temporary (ie, less than 4 months) depletion of IgG (up to 95% reduction of total IgG as seen with immunoadsorption) does not appear to impart an increased risk of infection (Eming, 2006; Furst, 2009; Keystone et al, 2007; Schmaldienst et al, 2001; van Vollenhoven et al, 2013). Study subjects will be monitored clinically for any infection. Further, commercial IVIG can be given to reverse the low IgG levels in case of a bacterial infection occurring while their IgG levels are decreased.

An antibody blocking FcRn is expected to also down modulate innate and adaptive immunity and the catabolism of IgG-containing immune complexes (IC). Specifically, it is expected that anti-FcRn will promote the clearance of IgG-containing ICs and the effects of these IC on stimulating innate immune cell production of inflammatory cytokines (e.g., IL-12, interferon-γ, and tumor necrosis factor [TNF]) and inhibit the processing and presentation of antigens contained within IC and thus the antigen-specific activation of CD4⁺ and CD8⁺ T-cells. Therefore, subjects with pre-existing conditions that are dependent upon IgG antibodies, such as chronic infections (e.g., HIV, HBV or HCV), will be excluded from this study, as will subjects with active infection in general.

SYNT001 administration could decrease the level of protective antibodies from prior vaccinations. Protective antibody levels for tetanus and varicella-zoster virus (chickenpox) are to be tested in accordance with Section 6.7.3.

10 CONCOMITANT MEDICATION AND TREATMENT

All treatments a subject receives within 14 days prior to enrollment through the end of the study will be documented. Concomitant medication and treatment for co-existing conditions, including those for pemphigus, are permitted if not excluded below. Topical antibiotics are permitted to treat active infections that occur on study. Topical or systemic treatments for oral candidiasis are permitted. Topical lidocaine for transient pain relief is acceptable as needed. Significant increases in anti-pemphigus medications will result in subjects being discontinued from the study. Concomitant treatment that is medically indicated for any AEs the subject experiences during the study are permitted

Use of the following treatments will not be permitted during the study unless otherwise specified:

- Rituximab or other anti-CD20 antibody
- Monoclonal antibodies other than study drug
- Any immunosuppressive drugs apart from corticosteroids, azathioprine, mycophenolate mofetil, or cyclosporine.
- Topical steroids
- Any dietary herbal supplements
- Any investigational drug or device
- Any vaccinations through Day 56. Following Day 56, subjects may be vaccinated at the discretion of the Investigator.

If over a period of at least two weeks on study drug, a subject on corticosteroids shows the absence of new lesions and significant healing of lesions that existed at study baseline, a slow corticosteroid taper may be started as per the following suggested schedule

- If on > 30 mg of prednisone per day, decrease by 10 mg every two weeks until a dose of 30 mg per day then decrease by 5 mg every two weeks
- If on < 30 mg of prednisone per day, decrease by 5 mg every two weeks

In cases in which concomitant medications are used, details to be recorded include the following: medication name, start date and time, stop date and time, dose, route, frequency, and reason for use. The concomitant medication names are to be coded using the World Health Organization

(WHO) Drug Dictionary (WHO-DD March 2013, Type B2 or later) and classified by anatomical therapeutic chemical (ATC) categories.

11 SAFETY

11.1 Safety Parameters

Clinical and laboratory AEs will be graded using the NCI CTCAE; Version 4.03 (See Appendix A).

Subjects will be monitored throughout the treatment and follow-up period for occurrence of AEs (acute, delayed, and/or cumulative), as well as for changes in clinical status, vital sign measurements, and laboratory data (including PD). Safety parameters to be measured/assessed include PEs, vital sign measurements, hematology, serum chemistries, urinalysis, and ECG.

11.2 Adverse Event Definition

An AE is defined as any untoward medical occurrence in a clinical trial subject associated with the use of a drug, whether considered drug related. An AE can be an unfavorable and unintended sign (e.g., an abnormal laboratory value finding), a symptom, or a disease temporally associated with the use of a drug, without judgment as to causality. An AE can arise from use of the drug (e.g., use in combination with another drug) and from any route of administration, formulation or dose, including an overdose. An AE also includes, but is not limited to, any clinically significant worsening of a pre-existing condition. Examples include:

- Any sign, symptom, physical finding, or laboratory result that has worsened in nature, severity or frequency compared to baseline;
- Reactions from an investigational drug, including those occurring because of an overdose, abuse of the study drug, withdrawal phenomena, sensitivity or toxicity;
- Concurrent illness that was not present or worsens in nature, severity, or frequency compared to baseline;
- Injury or accident; and/or
- Exacerbation of a pre-existing condition.

For data collection, all untoward events that occur after informed consent through the last study visit are to be recorded on eCRFs by the investigational site.

While pregnancy alone is not considered as an AE or SAE, any pregnancy complication(s) should be recorded as an AE(s) or SAE(s) (if applicable). Elective abortions without complications should not be regarded as AEs, unless they were therapeutic abortions (see below). Hospitalization for normal delivery of a healthy newborn should not be considered an SAE. If a female subject becomes pregnant during the conduct of the study, the Investigator must notify the Sponsor according to the procedures provided in Section 11.3.8).

11.3 Evaluating Adverse Events

The Investigator will determine the seriousness, intensity, and causality of an AE associated with the use of the study drug (i.e., events where there is a reasonable possibility that the event may have been caused by the study drug) based on the definitions that follow.

11.3.1 Serious Adverse Events

(Notify Medpace Safety within 24 hours; document on eCRF)

The SAE definition and reporting requirements are in accordance with Title 21 Part Code of Federal Regulations (CFR) 312.32 and the Guidance for Industry and Investigators Safety Reporting Requirements for Investigational New Drug (INDs) and Bioavailability /Bioequivalence Studies.

SAE: An AE is considered "serious" if, in the view of either the Investigator or sponsor, it results in any of the following outcomes:

• <u>Death:</u> This includes any death that occurs while the subject is "on study" through the last study visit.

Note: Death is an outcome of an AE, and not an AE. The event(s) that caused death (e.g., illness, accident) is the SAE. Death due to any other cause(s) must also be reported as an outcome of the reportable SAE.

- <u>Life-threatening adverse drug event:</u> An AE or suspected adverse reaction is considered "life threatening" if, in the view of either the Investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization:

In the absence of an AE, the Investigator should not report hospitalization or prolongation of hospitalization. This is the case in the following situations:

- Hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol
- Hospitalization or prolongation of hospitalization is part of routine procedure followed by study center

- Hospitalization for survey visits or annual physicals
- Hospitalization for observation with release within 24 hours

In addition, a hospitalization planned before the start of the study for a pre-existing condition, which has not worsened, does not count as an SAE.

• Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- Congenital anomaly/birth defect
- <u>Important medical event:</u> An event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

11.3.2 Overdose

An overdose is defined as a significant variation from the recommended/scheduled dosage for a product. The dosing for this study will be conducted in a controlled clinical setting and an overdose is not anticipated. However, in the event of an accident, for this study, an overdose of SYNT001 is considered a dose that is two-fold higher than the intended dose for the subject.

11.3.3 Non-Serious Adverse Events

(Document on eCRF)

All other AEs, not fulfilling the previous definitions, are classified as non-serious.

11.3.4 Protocol-Related Adverse Events

AEs that are not test drug related may nevertheless be considered by the Investigator or the Medical Monitor to be related to the conduct of the clinical study. That is, the event may be related to the fact that a subject is participating in the study. For example, a protocol-related AE may be an event that occurs during a screening period or that is related to a procedure required by the protocol.

11.3.5 Assessment of Causality

A medically qualified Investigator must assess the relationship of any AE (including SAEs) to the use of the investigational product, as related or not related, based on clinical judgment and using all available information, and may include consideration of the following factors:

- Possible alternative causes of the AE, including the disease under treatment, pre-existing conditions, concomitant use of other drugs, and presence of environmental or genetic factors.
- The temporal association between drug exposure and onset of the AE.
- Whether the manifestations of the AE are consistent with known actions or toxicity of the investigational product.
- The AE resolved or improved with decreasing the dose or stopping use of the investigational product (dechallenge). Judgment should be used if multiple products are discontinued at the same time.

The causal relationship between the study medication and the AE will be assessed using one of the following categories:

Not Related: Factors consistent with an assessment of Not Related include:

- Temporal relationship is lacking (e.g., the event did not occur within a reasonable time frame following administration of the study medication); or
- Other causative factors more likely explain the event (e.g., a pre-existing condition, other concomitant treatments).

Related: Factors consistent with an assessment of Related include:

- There is a positive temporal relationship (e.g., the event occurred within a reasonable time frame following administration of study medication); or
- The AE is more likely explained by the investigational product than by another cause (i.e., the AE shows a pattern consistent with previous knowledge of the investigational product or the class of the investigational product)

11.3.6 **Recording Adverse Events**

All AEs (including SAEs) are to be accurately recorded on the Adverse Event page of the subject's eCRF. The severity of each AE will be graded using the NCI CTCAE, Version 4.03. The date of onset as well as the end date of the event also should be recorded or the event should be entered as "ongoing". In addition, the method used to treat the AE and the outcome of the AE also will be noted. The Investigator will assess the relationship of the event to study drug.

11.3.7 **Planned Hospitalization**

A hospitalization planned by the subject prior to the first dose of study medication is considered a therapeutic intervention and not the result of a new SAE and should be recorded as medical

history. If the planned hospitalization or procedure is executed as planned, the record in the subject's medical history is considered complete. However, if the event/condition worsens during the trial, it must be reported as an AE.

11.3.8 Reporting Pregnancies

If a female subject or the female partner of a male subject becomes pregnant during the course of the study, the Investigator must report the pregnancy to the Medpace Safety using the **Pregnancy Reporting Form** within **24 hours** of becoming aware of the event. The Investigator must obtain consent to collect pregnancy information (including the status of the newborn, if applicable).

If some of the information required for completion of the Pregnancy Reporting Form is unavailable at the time of the initial report, follow-up reports will be completed and submitted within 24 hours of becoming aware of the new information. Any pregnancy will be followed through delivery for the observation of any SAEs. Any SAE that occurs during pregnancy must be recorded on the SAE report form in the EDC system (e.g., maternal serious complications, therapeutic or spontaneous abortion, ectopic pregnancy, stillbirth, neonatal death, congenital abnormality, birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs (See Section 11.3.9).

11.3.9 Serious Adverse Event Reporting

11.3.9.1 Governing Regulatory Requirements

Compliance with this request for prompt reporting is essential in that the sponsor is responsible for informing the US Food and Drug Administration (FDA) and other regulatory authorities as well as all other participating Investigators of the event.

Under FDA ruling (US Code of Federal Regulations, Title 21 CFR Part 312.32) and the ICH Guidelines for Clinical Safety Data Management Definitions and Standards for Expedited Reporting, the sponsor is required to submit written documentation, in the form of a safety report, detailing:

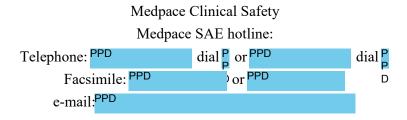
- Any event associated with the use of the drug, that is both <u>serious and unexpected</u>, or
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.

Written submission must be made by the sponsor to the FDA and the IRBs as soon as possible and in no event later than 15 calendar days after the sponsor's initial notification of the event. The sponsor shall also inform all Investigators.

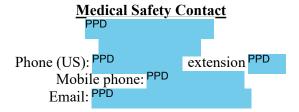
11.3.9.2 Time Frame for Reporting

Any death, SAE, pregnancy, or unexpected (and severe) AE experienced by the subject after informed consent through the last study visit, regardless of relationship to study drug, , must be promptly reported (within 24 hours of the Investigator becoming aware of the event) by telephone or electronic transmission to the sponsor (or designee).

Contact information for **SAE** reporting:



Additionally, the Investigator will be able to contact the **Medical Monitor**:



11.3.9.3 Information to be Provided by the Investigator

SAEs must be recorded on the SAE form in the EDC system. This requirement includes all SAEs that occur after informed consent through the last study visit.

The minimum information required for SAE reporting includes identity of Investigator, site number, subject number, an event description, SAE term(s), onset date, the reason why the event is serious (i.e., the seriousness criteria) and the Investigator's assessment of the relationship of the event to study treatment. Additional SAE information including medications or other therapeutic measures used to treat the event, action taken with the study treatment due to the event, and the outcome/resolution of the event will be recorded. Paper forms for reporting SAEs will be provided to the study sites as back-up in case the EDC system is not accessible.

In all cases, the Investigator should continue to monitor the clinical situation and report all material facts relating to the progression or outcome of the SAE. Furthermore, the Investigator may be required to provide supplementary information as requested by Syntimmune or designee.

When reporting an SAE, the following additional points should be noted:

When the diagnosis of an SAE is known or suspected, the Investigator should report the
diagnosis or syndrome as the primary SAE term, rather than as signs or symptoms. Signs
and symptoms may then be described in the event description. For example, dyspnea
should not be used as an SAE term if the diagnosis, which caused the dyspnea, is known
to be malignant pleural effusion.

- Death should not be reported as an SAE, but as an outcome of a specific SAE, unless the event preceding the death is unknown. In the exceptional case where the events leading to death are unknown, then death may be used as an event term. If an autopsy was performed, the autopsy report should be provided.
- While most hospitalizations necessitate reporting of an SAE, some hospitalizations do not require SAE reporting, as follows:
 - Elective or previously scheduled surgery, e.g., a previously scheduled ventral hernia repair
 - Procedures for pre-existing conditions that have not worsened after initiation of treatment
 - Pre-specified study hospitalizations for observation
 - Events that result in hospital stays of less than 24 hours and that do not require admission, e.g., an emergency room visit for hematuria that results in a diagnosis of cystitis and discharge to home on oral antibiotics
- SAEs must, however, be reported for any surgical or procedural complication resulting in prolongation of the hospitalization.

11.3.10 Regulatory Reporting

Syntimmune (or designee) will process and evaluate all SAEs as soon as the reports are received. For each SAE received, Syntimmune will decide as to whether the criteria for expedited reporting have been met.

Syntimmune (or designee) will submit SAEs that meet the criteria for expedited reporting to the regulatory authorities in accordance with local regulations governing safety reporting. Reporting of SAEs by the Investigator to his or her IRB will be done in accordance with the standard operating procedures and policies of the IRB. Adequate documentation must be maintained showing that the IRB was properly notified.

11.3.11 Follow-up Information on a Serious Adverse Event (SAE)

Appropriate diagnostic tests should be performed and therapeutic measures, if indicated, should be instituted. Appropriate consultation and follow-up evaluations should be carried out until the event has returned to baseline or is otherwise explained by the Investigator.

If all required information on the SAE form is not available at the time of the initial report, follow-up information will be completed in the EDC system.

11.4 Other Safety Considerations

11.4.1 Laboratory Data

All laboratory data obtained during the study should be reviewed. Any abnormal value that leads to a change in subject management (e.g., requirement for additional medication or monitoring) or is of clinical significance by the Investigator should be reported as an AE and/or SAE as appropriate, unless this value is consistent with values obtained before entry into the study.

11.4.2 Medication Errors

Any medication error that results in an AE, even if it does not meet the definition of serious, requires reporting within 24 hours to the safety Medical Monitor.

11.4.3 Follow-Up of Adverse Events

Any SAE or AE assessed as related to study drug must be followed until either resolution of the event or determination by the Investigator that the event has become stable or irreversible. The Investigator will follow all drug related AEs until there is a return to the subject's baseline condition, or until a clinically satisfactory resolution has been achieved. The appropriate follow-up visits must be scheduled and the specific tests repeated or performed as necessary. The status of all AEs will be documented as of the last study visit.

Where a diagnosis is possible, it is preferable to report this diagnosis rather than a series of terms (signs/symptoms) relating to the diagnosis.

11.5 Safety Monitoring for Dose Escalation

Following dosing in each cohort, all safety/tolerability data (e.g., PEs, vital signs [including pulse oximetry], clinical safety laboratory tests, ECGs and AE/SAE assessments) as well as any available and relevant PD data collected through Day 42 will be reviewed by the DEC. A decision to escalate to the next cohort will be made. The recommendation may be to continue to

the next scheduled dose level, discontinue the study or to modify dosing to a dose less than the current dose or higher than the current dose but lower than the next planned dose.

12 STATISTICAL CONSIDERATIONS

All descriptive and inferential statistical analyses will be performed using the most recently released and available Statistical Analysis System (SAS) software, unless otherwise noted. Missing data will not be imputed unless otherwise stated. All clinical data captured will be provided in data listings. A Statistical Analysis Plan (SAP) and a Pharmacokinetic Analysis Plan (PAP) will be finalized prior to database lock.

12.1 General Design

All data for enrolled subjects will be presented in data listings by subject number.

Continuous data will be described using descriptive statistics: number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Frequencies and percentages will be used for summarizing discrete (categorical) data. When categorical data are presented, the percent will be suppressed when the count is zero to draw attention to the non-zero counts. The denominator for all percentages, unless otherwise specified, will be the number of subjects in the specified analysis population.

12.2 Sample Size Justification

Formal sample size calculations were not performed. The number of subjects was chosen based on feasibility and was considered sufficient to meet the study objectives.

12.3 Statistical Considerations

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP). The SAP may modify the plans outlined in the protocol; any deviations from the previously described statistical plan will be described and justified in an SAP amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate and will be described in the SAP. Methods of handling of missing data for different endpoints will be further specified in the SAP. In general, where individual data points are missing because of insufficient samples, dropouts, or other reasons, the data will be analyzed based on reduced denominators unless specified otherwise in the SAP.

Results will be summarized by cohorts.

12.3.1 Study Populations

Three populations will be employed in the analysis of study data:

• The **intent-to-treat (ITT)** population will consist of all subjects who have received at least one dose of study drug. All safety analyses will be performed on the ITT population.

- The **PK** population will consist of all subjects who receive at least one dose of study drug and have sufficient post-dose blood samples to obtain PK parameters.
- The **PD** population will consist of all subjects who receive at least one dose of study drug and have post-dose PD data available.

Primary safety analyses will be performed on the ITT population. Demographics, subject disposition, and screening and baseline characteristics will be summarized for the ITT, PK, and PD populations, where appropriate.

12.3.2 Subject Accountability, Demographics, and Baseline Characteristics

Subject disposition, demographic information and baseline characteristics will be presented. Any discrepancy between treatment to be given and treatment received will be accounted for in these displays.

12.3.3 Concomitant Medications

Concomitant medications will be coded using WHO Drug Dictionary (WHO-DD March 2013, Type B2 or later) and the data will be summarized and presented in tables and listings.

12.4 Planned PK Analysis

Study drug concentrations will be used to calculate the following PK parameters: $t_{1/2}$, C_{max} , T_{max} , and AUC_{0-24} and $AUC_{0-\infty}$. PK parameters will be determined using noncompartmental method(s). Descriptive statistics of PK parameters for SYNT001 will include mean, SD, coefficient of variation (CV), median, minimum, and maximum. T_{max} will be reported as median and range. All descriptive statistics will be performed on untransformed PK parameters and after log_{10} transformation of PK parameters.

For calculation of mean concentrations and generation of mean concentration-time profiles, all below the limit of quantification (BLQ) values will be set to zero except when an individual BLQ falls between 2 quantifiable values, in which case it will be omitted.

If there are values above the BLQ, but too sparse to allow full analysis, descriptive statistics will be performed on available values.

12.5 Safety Data

Safety observations and measurements include AEs, safety laboratory tests, vital sign measurements, PEs, and ECGs.

Treatment-emergent AEs will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA®; Version 19 or higher) System Organ Class (SOC) and preferred term, classified from verbatim terms. The incidence and percentage of subjects with at least 1 occurrence of a preferred term will be included, using the most severe grade. The number of events per preferred term will also be summarized. Causality (relationship to study treatment) will be summarized separately.

AEs, SAEs, and AEs leading to withdrawal, dose modification, or treatment discontinuation will be listed by subject, cohort, and overall per SOC and preferred terms. Duration of AEs will be determined and included in listings, along with action taken and outcome.

Laboratory results will be summarized by cohort. Incidence of laboratory abnormalities will be summarized. The worst on-study grade after the first dose of study drug will be summarized. Results for variables that are not coded will be presented in the listings as below, within, and above the normal limits of the local laboratory.

Vital sign measurements and change from baseline will be summarized at each scheduled time point by cohort using descriptive statistics.

Arithmetic mean of parameters from triplicate ECG will be calculated first for each participant at each planned time point. Then summary statistics of ECG test parameters (mean of triplicate) and change from baseline to each post-dose time point will be calculated. Shift tables for ECG test result category change (normal, abnormal, clinically abnormal) from pre-dose to each post-dose time point showing number and percentage of subjects with movement between categories will be presented by treatment group. Frequency and percentage of subjects experiencing potential QTc prolongation (QTcF > 450) will be summarized at each time point by cohort.

12.6 Pharmacodynamic/Activity Data

PD results will be summarized by cohort.

12.7 Immunogenicity Data

Immunogenicity results will be summarized by cohort.

12.8 Interim Analysis

No interim analysis is planned. Safety results will be examined for making dose-escalation decisions; no statistical analyses are planned for aiding these dose-escalation decisions.

13 DATA QUALITY ASSURANCE

All data will be entered in a validated electronic data capture system using single data entry. Standard procedures (including following data review guidelines, manual clinical review based on subject profiles, computerized validation to produce queries, and maintenance of an audit file which includes all database modifications) will be followed to ensure accurate data. Clinical personnel will review all data listings for outliers, data inconsistencies, and spelling errors.

During the study, a study site monitor will make site visits to review protocol compliance, compare electronic case report forms (eCRFs) against individual subject medical records, assess drug accountability, and ensure that the study is being conducted using pertinent regulatory requirements. eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that subject confidentiality is maintained. Checking the eCRFs for completeness, clarity and cross checking with source documents is required to monitor the progress of the study. Direct access to source data is also required for inspections and audits, and will be carried out giving due consideration to data protection and medical confidentiality. Each Investigator will have assured Syntimmune of full access to complete source data for study participants and associated necessary support at all times.

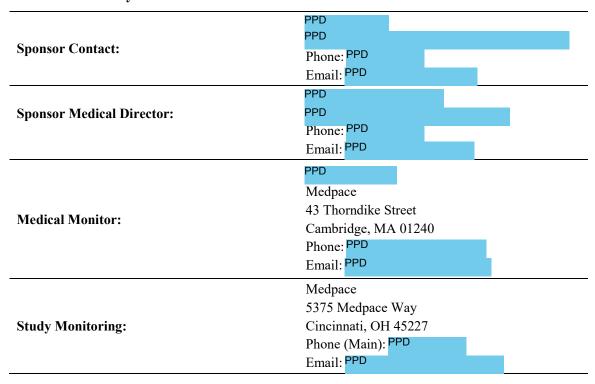
In addition to routine monitoring procedures, audits of clinical research activities in accordance with standard operating procedures (SOPs) may be performed to evaluate compliance with the principles of GCP. A regulatory authority may also wish to conduct an inspection (during the study or even after its completion). If a regulatory authority requests an inspection, the Investigator must immediately inform Syntimmune that this request has been made. Study conduct may be assessed during the study by a Clinical Quality Assurance representative(s) to ensure that the study is conducted in compliance with the protocol. This designee, as well as the site monitor, will be permitted to inspect the study documents (study protocol, eCRFs, investigational product accountability, original study-relevant medical records). All subject data will be treated confidentially. During the clinical study, access will be available to Syntimmune or their designee (e.g., contract research organization [CRO]) to view the eCRFs after completion of the individual sections of the study. Furthermore, the study protocol, each step of the data-recording procedure and the handling of the data as well as the study report may be subject to independent review by a Quality Assurance representative. Clinical site and study audits will be conducted as necessary to assure the validity of the study data.

14 STUDY ADMINISTRATION

14.1 Study Administrative Structure

The study administration structure is provided in Table 6.

Table 6: Study Administrative Structure



14.2 Ethical Conduct of the Study

The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH E6 Tripartite Guideline (January 1997), and in general, be conducted in a manner consistent with the principles described in the Declaration of Helsinki. The Investigator will ensure that the conduct of the study complies with the basic principles of GCP as outlined in the current version of 21 CFR, subpart D, Part 312, "Responsibilities of Sponsors and Investigators", Part 50, "Protection of Human Subjects", and Part 56, "Institutional Review Boards".

14.3 Informed Consent (ICF)

A properly executed, written informed consent document, in compliance with 21 CFR, Part 50 and the ICH guidelines, will be obtained from each subject before the subject is entered into the study and before any study screening procedure is performed that involves risk. Attention will

be directed to the basic elements required for incorporation into the informed consent under US Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a]) and (21 CFR 50.25[b]), as necessary.

Sample ICFs will be supplied to each site. Syntimmune or its designee must review any proposed deviations from the sample ICF. The final IRB-approved document must be provided to Syntimmune for regulatory purposes.

It is the responsibility of the Investigator, or a person designated by the Investigator, to obtain written informed consent from each subject (or the subject's legally authorized representative) participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. In the case where the subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the subject has orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. A copy of the ICF must be provided to the subject or to the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

The eCRF for this study contains a section for documenting informed subject consent, and this must be completed appropriately. Signed ICFs must remain in each subject's study file and must be available for verification by site monitors at any time. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated as necessary. All subjects (including those already being treated) should be informed of the new information, should be given a copy of the revised form, and should give their consent to continue in the study.

14.4 Institutional Review Board

This study is being conducted under US IND 128152. This protocol (and any modifications) and appropriate consent procedures must be reviewed and approved by an IRB. This board must operate in accordance with the current federal or local regulations. The Investigator will send a letter or certificate of IRB approval to Syntimmune (or designee) before subject enrollment and whenever subsequent modifications to the protocol are made.

14.5 Dose Escalation Committee

The DEC will be responsible for confirming the safety of the investigative product prior to dose escalation, as well as the dose level for each successive cohort. In addition, over the course

of the study, the DEC will review any drug-related SAEs to determine if modifications to the study or other measures are necessary to ensure the safety of the subjects. The DEC will consist of the Medical Monitor, an Independent Clinical Expert and a Syntimmune Medical Officer. To assist in the safety assessments, the DEC may request that Investigators, other experts, or members within their organizations review the data and participate in the discussions.

14.6 Future Use of Subject Samples

Not all the tissue and blood components obtained during this study may be required for the tests that are part of the clinical trial. Available samples may be used for additional research. This research will help to understand disease subtypes, drug response and AE, and possibly identify new drug targets or biomarkers that predict subject response to treatment. The use of the samples for internal research will be done using the guidelines defined by the FDA guidance for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individual Identifiable (issued 25 April 2006) and the European Medicines Agency (EMA) Reflection Paper on Pharmacogenetic Samples, Testing and Data Handling (Doc. Ref.

EMEA/CHMP/PGxWP/201914/2006; 15 November 2007). If a subject requests destruction of their tissue and blood samples and the samples have not yet been de-identified, Syntimmune will destroy the samples as described in this FDA guidance. Syntimmune will notify the Investigator in writing that the samples have been destroyed.

15 CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications to ongoing studies must be made only after consultation between a Syntimmune representative and the Investigator. Protocol modifications will be prepared, reviewed, and approved by Syntimmune representatives.

All protocol modifications must be submitted to the IRB for information and approval in accordance with local requirements, and to regulatory agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study subjects, or when the change involves only logistical or administrative aspects of the trial (e.g., change in site monitor, change of telephone number).

16 CONDITIONS FOR TERMINATING THE STUDY

Syntimmune has the right to terminate the study at any time. In terminating the study, Syntimmune and the Investigator will ensure that adequate consideration is given to the protection of the subjects' interests.

17 STUDY DOCUMENTATION, CRFS, AND RECORD KEEPING

17.1 Investigator's Files and Retention of Documents

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into 2 separate categories as follows: (1) Investigator's study file and (2) subject clinical source documents.

The Investigator's study file will contain the protocol and protocol amendments, eCRFs, query forms, IRB and governmental approval with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Subject clinical source documents (usually predefined by the project to record key efficacy and safety parameters independent of the eCRFs) may include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalogram, X-ray, pathology and special assessment reports, signed ICFs, consultant letters, and subject screening and enrollment logs. The Investigator must keep these 2 categories of documents on file for at least 2 years following the marketing application approval date for the study treatment and for the indication being investigated or for 2 years after the development program is discontinued and the FDA notified. After that period, the documents may be destroyed subject to local regulations with prior written permission from Syntimmune. If the Investigator wants to assign the study records to another party or move them to another location, Syntimmune must be notified in advance.

If the Investigator cannot guarantee the archiving requirement at the study site for any or all of the documents, special arrangements must be made between the Investigator and Syntimmune to store these in a sealed container outside of the study site so that they can be returned sealed to the Investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the study site.

17.2 Source Documents and Background Data

Investigators must maintain adequate and accurate source documents on which the eCRFs for each subject are based. They are separate and distinct from the eCRFs.

These records include detailed notes on the following:

- Medical history
- Date and time of informed consent with Health Insurance Portability and Accountability
 Act (HIPAA) authorization either contained in the ICF or presented to the subject
 candidate as a standalone document
- Description of the complete consenting process
- The basic identifying information that linked the subject's medical record with the eCRFs
- The results of all diagnostic tests performed, diagnoses made, therapy provided, and any other data on the condition of the subject
- The medical condition of the subject during their involvement in the study
- All AEs
- The subject's exposure to the study medication
- The subject's exposure to any concomitant therapy
- All relevant observations and data on the condition of the subject throughout the trial
- Justification for all entries in the subject's eCRF

A subject log of all potentially eligible subjects considered, but not consented, for obvious deviations from the entry criteria, will be kept at each site. The log will contain subjects' initials, diagnosis, eligibility, or, if not eligible, reason for not consenting. All consented subjects will be logged, regardless of whether they ultimately enroll.

Upon request, the Investigator will supply Syntimmune with any required background data from the study documentation or clinic records. This is particularly important when eCRFs are illegible or when errors in data transcription are suspected. In case of special problems or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

17.3 Audits and Inspections

The Investigator should understand that source documents for this study should be made available to appropriately qualified personnel from Syntimmune (or designee), or to health authority inspectors after appropriate notification. The verification of the eCRF data must be by direct inspection of source documents.

17.4 Electronic Case Report Forms

Clinical trial data for this study will be captured on eCRF designed for computer processing and analysis. This computerized system will be validated and compliant with 21 CFR Part 11. Corrections to data will be made using 21 CFR Part 11, Electronic Records; Electronic Signatures. If corrections are made after review and sign-off by the Investigator, he/she must be aware of the changes and provide written acknowledgement. There will also be an electronic audit trail. Corrections on paper CRFs must be initialed and dated by the person making the change. The Investigator agrees to provide all information requested on the eCRF in an accurate manner using instructions provided. The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to Syntimmune in the eCRF and in all required reports.

An eCRF is required to be submitted for every subject who receives any amount of study drug. This includes submission of retrievable data on subjects who withdraw before completion of the study. Prior to submission, eCRFs must be reviewed for completeness and accuracy, and signed and dated where either indicated, by the Principal Investigator or authorized delegate from the study staff. If a subject stops treatment or terminates from the study, the dates and reasons must be noted on the eCRF.

18 MONITORING THE STUDY

It is understood that the responsible Syntimmune site monitor (or designee) will contact and visit the Investigator regularly and will be allowed on request to inspect the various records of the trial (eCRFs and other pertinent data) if subject confidentiality is maintained in accordance with local requirements.

It will be the site monitor's responsibility to inspect the eCRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The site monitor should have access to laboratory test reports and other subject records needed to verify the entries on the eCRF. The Investigator (or designee) must agree to cooperate with the site monitor to ensure that any problems detected during these monitoring visits are resolved.

19 CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The Investigator must ensure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On eCRFs or other documents submitted to Syntimmune, subjects should be identified by an identification code and not by their names. The Investigator should keep a subject enrollment log showing codes, names, and addresses. The Investigator should maintain documents not for submission to Syntimmune (e.g., subjects' written consent forms) in strict confidence.

Authorized regulatory officials and Syntimmune personnel (or their representatives) will be allowed full access to inspect and copy the records. All study drugs, subject bodily fluids and tissue, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by Syntimmune.

The Principal Investigator also agrees that all information received from Syntimmune, including but not limited to the IB, this protocol, eCRFs, the INDs, and any other study information remain the sole and exclusive property of Syntimmune during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The Principal Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

20 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. The Investigator agrees that any manuscript or abstract they author may be published only after receiving written permission from Syntimmune.

If Syntimmune coordinates a publication or presentation of study results from all study sites, the participation of Investigator or other representatives of study site as a named author shall be determined in accordance with Syntimmune policy and generally accepted standards for authorship.

21 REFERENCES

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Appendix A: NCI CTCAE, Version 4.03

Appendix B: Pemphigus Disease Area Index (PDAI)

Pemphigus Disease Area Index (PDAI)

Skin	Activity		Damage
Anatomical Locatio	-		Post-inflammatory hyperpigmentation or erythema from resolving lesion
	0 absent 1 1-3 lesions, up to one >2 cm in any diameter, none > 6 cm 2 2-3 lesions, at least two > 2 cm diameter, none > 6cm 3 >3 lesions, none > 6 cm diameter 5 >3 lesions, and/or at least one >6 cm 10 >3 lesions, and/or at least one lesion >16 cm diameter or entire area		0 absent 1 present
Ears			
Nose			
Rest of the face			
Neck			
Chest			
Abdomen			
Back, buttocks			
Arms			
Hands			
Legs			
Feet Genitals			
	/120		/12
Total skin	/120		712
Scalp	-		Doct inflammaton
Scalp	Erosion/Blisters or new erythema		Post-inflammatory hyperpigmentation or erythema from resolving lesion
	0 absent 1 in one quadrant 2 two quadrants 3 three quadrants 4 affects whole skull 10 at least one lesion > 6 cm		0 absent 1 present
Total Scalp (0-10)	/10		/1
Mucous mer	nbrane		
Anatomical Location	Erosion/Blisters		
	0 absent 1 1 lesion 2 2-3 lesions 5 >3 lesions or 2 lesions >2 cm 10 entire area	Number lesions if ≤ 3	
Eyes		\sqcup	
Nose			
Buccal mucosa			
Hard palate		\vdash	
Soft palate		\vdash	
Upper gingiva		\vdash	
Lower gingiva		\vdash	
Tongue		\vdash	
Floor of mouth		\vdash	
Labial bucosa		\vdash	
Posterior pharynx		\vdash	
A			
Anogenital Total Mucosa	/120		

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Syntimmune, Inc.

SUMMARY OF CHANGES TO CLINICAL STUDY PROTOCOL

A Phase 1b, Multicenter, Open-Label, Safety, Tolerability, and Activity Study of SYNT001 in Subjects with Chronic Pemphigus (Vulgaris or Foliaceus)

Protocol Number: SYNT001-103

IND Number: 132727

Study Drug: SYNT001

Sponsor: Syntimmune, Inc.

257 Park Avenue South

15th Floor

New York, NY 10010

Medical Monitor: PPD

43 Thorndike Street, Cambridge, MA 01240

Phone: PPD extension PPD

Mobile: PPD

Date of Protocol: Original, 18 January 2017

 Amendment 1.1
 21 March 2017

 Amendment 2.0
 12 April 2017

Confidentiality Statement

The information contained herein is confidential and the proprietary property of Syntimmune, Inc. and any unauthorized use or disclosure of such information without the prior written authorization of Syntimmune is expressly prohibited.

SUMMARY

The SYNT001-103 protocol has been amended under version 2.0 as follows:

- Lengthened subject follow-up to include study visits at Day 84 and Day 112 to follow pharmacodynamics (Serum IgG) and clinical effects out to 12 weeks from the last dose of SYNT001
- Added immune phenotyping to Day 56 assessments
- Contraception requirement in Inclusion and Exclusion criteria updated to correspond to additional study visits (out to Study Day 112; 12 weeks following last dose of SYNT001) for both females and males
- Total blood draw for subjects completing the study at Day 112 updated to approximately 381 mL from 311 mL in Section 6.7
- Allowing vaccinations at the discretion of the Investigator after Day 56
- AE reporting timelines updated to correspond to additional study visits
- Clarifying language for Tetanus and Varicella-Zoster Virus antibody testing follow-up,
 specifying the actual study visit Days when additional testing will be performed
- Clarifying language for Investigator removal of subjects from study to not require consultation with Medical Monitor but to allow it if desired
- Clarifying language for dose escalation stopping rules; rules for stopping escalation are not changed
- Additional text related to potential immune effects and corresponding references added
- Various typographical and formatting corrections as well as corrections for consistency made throughout the document.

SPECIFIC CHANGES

Text deletions are shown using strike through font; new text added in *italic font*.

SECTION 1, STUDY SYNOPSIS

In addition to the changes in the section below, the synopsis has been updated to reflect all changes in the body of the protocol.

Duration of subject participation and duration of study

• Up to 70-126 days (40 18 weeks): Screening of up to 2 weeks (14 days); Treatment dosing period of 8 weeks (56 days) 28 days; Follow-up period of and 4 8 weeks (56 28 days)

Table 1, Schedule of Assessments

- Table updated to show Treatment Period spanning Day 0 through Day 56
- Table updated to show Follow-up Period spanning Day 84 through Day 112
- Table updated by adding a Day 84 visit and a Day 112/ Early Termination visit, with associated assessments described in Section 7
- Adverse Events and Concomitant Medications:
 - To be collected from the date that the ICF was signed through the last study visit until 28 days after the last dose of study drug

• Footnote d: Clinical safety labs:

O Hematology, clinical chemistry, and urinalysis (see Section 6.6 for a complete list). Full clinical safety lab draws will be collected at Screening and on Days 0, 7, 14, 21, 28, 33, 42, 56, 84 and 11256. PD biomarkers (albumin levels, hematocrit, hemoglobin, platelet count, reticulocyte count, LDH, and total and direct bilirubin) will be derived from the clinical safety laboratory results.

Footnote e: Pregnancy Test:

To be performed at time of screening, prior to first dose of SYNT001 on Day 0
 and on Days 56 and 112 (urine or serum test is acceptable however, positive urine tests must be confirmed with serum testing.)

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• Footnote g: Serology:

Testing at Day 56 will not be done for any subject whose baseline titer is below the level of detection. If the Day 56 results are greater than 30% below the baseline value, or if the subject falls below the level of detection, the subject will be re-tested at *Day 841* month after the Follow Up visit (approximately 2 months after the subject's last dose); if still below the baseline value (or level of detection), the subject will be re-tested at *Day 112* after another month (3 months after last dose). Any subject whose baseline value for tetanus or VZV was above the detectable level at baseline, and is not within 30% of the baseline value or is below the detectable level *by Day 112* on Day 56 and upon 2 retests (2 and 3 months following last dose of SYNT001), will be referred to their primary care physician for further management. See Section 6.7.3 for additional information.

• Footnote i: Immunogenicity:

- Blood samples will be collected pre-dose when collected on dosing days.
 Samples will be collected on Days 0, 14, 28, 56, 84 and 112. See Section 6.7.6 for additional information.
- Footnote q: Subjects will return to the clinic on Days 84 and 112 for follow-up visits. Subjects whose total IgG is not within 30% of their Day 0 baseline value and not above 500 mg/dL at the Day 112 visit will be referred for further management. Extended follow-up visits will occur only if additional testing for anti-tetanus and/or anti-VZV titers are required. These visits will occur as needed at approximately 2 months post last dose and 3 months post last dose.

SECTION 4 STUDY DESIGN

Section 4.3, Overview of Study Design

- On Day 0 photographs will be taken of active lesions. Follow-up photographs will be taken of the same areas on Days 33, and 56, 84, and 112. If a subject begins a steroid taper, additional photographs will be taken at the clinic visit during which the decision to begin the taper is made.
- Subsequent visits will occur on Days 1, 2, 5, 7, 12, 14, 19, 21, 28, 29, 30, 33, 42 and 5642 for safety assessments, study drug dosing, sample collections, and other study procedures.
- Subjects also will return to the clinic on Days 84 and 112 for follow-up visits. Subjects whose total IgG is not within 30% of their Day 0 baseline value and not above 500 mg/dL at the Day 112 visit will be referred for further management. 56 (28 days after receiving their last dose of study drug) for an End of Study/Follow Up visit.
- **Note**: No vaccinations may be given from within 2 weeks of screening *through Day 56*. Following Day 56, subjects may receive vaccinations at the discretion of the Investigator. until 2 months following the last dose of study drug

SECTION 5 STUDY POPULATION

Section 5.1, Target Population

• This study will be conducted in approximately 16 male and female subjects (2 cohorts of 8 subjects each) with a confirmed diagnosis of pemphigus (vulgaris or foliaceus); however, a third cohort of up to 8 subjects may be added. Subjects will be enrolled only once in the study and will not be included in subsequent dosing cohorts. Subjects who withdraw for any reason other than an AE and who do not receive study drug or have only received one dose of study drug may be replaced, up to one subject per cohort. Subjects who do not receive all doses of study drug will continue to be followed through all scheduled visits28 days after last dose. The maximum number of subjects who may be enrolled in this study is 27 (24 + up to 3 replacements, as necessary). Within each dosing cohort, no more than 3 subjects may be enrolled with pemphigus foliaceus.

Section 5.2, Inclusion Criteria

7. Females of childbearing potential must agree to be abstinent or else use any two of the following medically acceptable forms of contraception (<1% per year failure rate) from

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- the Screening Period through 30 days after the final dose of study visit drug: oral contraceptive, condom with or without spermicidal jelly, diaphragm or cervical cap with spermicidal jelly, or intra-uterine device (IUD). A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception.
- 9. Males with female partners of childbearing potential, including males who are surgically sterile (post vasectomy), must agree to be abstinent or else use a medically acceptable form of contraception from the screening period through 60 days after the final dose of study visit drug.

SECTION 6 STUDY PROCEDURES

Section 6.6, 12-Lead Electrocardiogram (ECG)

• Digital 12-lead ECG measurements will be obtained at screening, on Days 0 and 28 at 5 minutes after the completion of the infusion and at the Day 56 (Follow up) visit. Subjects who conduct their Day 12 visit at the investigative site, as opposed to an athome nurse visit, will have an additional ECG performed. ECGs are to be performed with the subject in a supine position having rested in this position for at least 5 minutes before each reading. ECGs are to be performed in triplicate, each 1–2 minutes apart. See Table 2 for timing window allowances with respect to performing ECG.

Section 6.7, Clinical Laboratory Measurements

- Laboratory testing (hematology, urinalysis, serum chemistry, virology, serology, pregnancy tests, PD samples, PK samples, and anti-drug antibody samples) will be performed using established methods by a central laboratory. Safety laboratory panels are defined as listed in Table 3. Blood and urine samples for hematology, serum chemistry, and urinalysis will be prepared using standard procedures. Results will be provided to the Investigator. Aliquots from the PK, biomarker and anti-drug antibody samples may be retained as back-up for additional testing as necessary. Subjects will be in a seated or supine position during blood collection. Full clinical safety lab draws will be collected at Screening and on Days 0, 7, 14, 21, 28, 33, 42, 56, 84 and 11256. The total blood draw for each subject who completes the study at Day 11256, will be approximately 311 381 mL. Please refer to the Laboratory Manual for more information.
- Table 3: Clinical Laboratory Panels, Hematology
 - o CBC with differential and blood smear

Section 6.7.1 Pregnancy Testing

• Pregnancy testing will be performed for women of childbearing potential at screening and prior to first dose of SYNT001 on Day 0 and Days 56 and 112 (urine or serum test is acceptable however, positive urine tests must be confirmed with serum testing.)

Section 6.7.3. Serum Tetanus Antibody and Varicella-Zoster Virus Antibody Testing

• Samples for serum tetanus antibody and Varicella-Zoster virus antibody testing are to be collected at baseline (pre-dose, Day 0) and on Day 56 (Follow-Up visit). Testing at Day 56 will not be done for any subject whose baseline titer is below the level of detection. Specifically, if the baseline VZV titer is above the detectable level, but Tetanus is not, only the VZV antibody titer will be tested on Day 56. If the Day 56 results are below the baseline value, defined as greater than 30% below the baseline value, or if the subject falls below the level of detection, the subject will be re-tested at Day 841 month after the Follow Up visit (approximately 2 months after the subject's last dose); if still below the baseline value (or level of detection), the subject will be re-tested at Day 112after another month (3 months after last dose). Any subject whose baseline value for tetanus or VZV was above the detectable level at baseline, and is not within 30% of the baseline value or is below the detectable level by Day 112on Days 56 and upon 2 retests (2 and 3 months following last dose of SYNT001), will be referred to their primary care physician for further management

Section 6.7.5 Pharmacodynamic (PD) Sampling

Table 1: Pharmacodynamic/ Activity Assessments

Parameter	Collection Timepoints
IgG, IgG subtypes (IgG1-4), IgA, IgM	Screening, and Days 0, 1, 2, 5, 7, 12, 14, 19, 21, 28, 29, 30, 33, 42, 56, 84 and 11256.
Circulating immune complexes (CIC)	Days 0, 5, 7, 12, 14, 19, 21, 28, 33, 42, 56, 84 and 11256
• Albumin	Screening, and Days 0, 7, 14,21, 28, 33, 42, 56, 84 and 11256
Anti-Dsg (1 and 3) antibody titer	Screening, Days 0, 7, 14, 33, 56, 84 and 11256
 Complement component 3 (C3) Anti-epithelial cell antibody (AECA) levels by indirect immunofluorescence 	Days 0, 14, 33, 56, 84 and 112 56
Exploratory biomarker (RNAseq, Urine IgG)	Days 0, 14, 33, 56, 84 and 112 56
Immune phenotyping by flow cytometry for measurement of CD3 ⁺ CD4 ⁺ T, CD3 ⁺ CD8 ⁺ T, monocytes, NK cells and B cells	Days 0, 28 and 2856
Exploratory biomarker (FCGR2A SNP)	Day 0

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Section 6.7.6 Immunogenicity Testing

• Up to 4 sSerum samples will be collected for immunogenicity analyses. Samples will be collected on Days 0 (pre-dose), 14, 28, 56, 84 and 56112

Section 6.9 Prior and Concomitant Medication

 All medications a subject receives within 14 days prior to enrollment through the end of the study (Day 56) will be documented on the source document and eCRF.

Note: No vaccinations may be given from within 2 weeks of screening *through Day 56*. Following Day 56, subjects may receive vaccinations at the discretion of the Investigator. until 2 months following the last dose of study drug.

Section 6.10 Adverse Events Assessments

• Information regarding the occurrence of AEs will be collected from the time the subject signs the informed consent form *and is continuing through the last study visit* throughout their participation in the study, including a period of 28 days after study drug dosing. Findings at screening and Day 0 (pre-dose) will be recorded as medical history. Any known untoward event that occurs beyond the AE reporting period that the Investigator assesses as related to study drug also should be reported as an AE

Section 6.11 Photographs

• On Day 0 photographs will be taken of active lesions. Follow-up photographs will be taken of the same areas on Days 33, 56, 84 and 11256. Subjects who begin a steroid taper will have additional photographs taken at the clinic visit during which the decision to begin the taper is made. A separate manual describing the procedures for taking photographs will be provided.

Section 6.12 Skin Biopsies

• Optional skin biopsy samples will be collected on Day 0 pre-dose and on Days 1, 2, 14, 33, *56* and *8456* to analyze SYNT001 levels

SECTION 7 STUDY ASSESSMENTS

Section 7.7 Dose 2 Follow-up Day 12

• On Day 12 (\pm 6 hours) the subject *may* will return to the clinic, or be visited by an athome nurse, and the following procedures are to be performed:

Section 7.11 Treatment Day 28 (Dose 5)

• On Day 28 (± 6 hours 1 Day), subjects will return to the clinic and the following procedures are to be performed prior to study drug infusion:

Section 7.15 Follow-up Day 42

• PDAI Score (Section 6.4)

Section 7.16 Follow-up Day 56 (End-of-Study) or Early Termination Visit

- 12-Lead ECG (to be obtained in triplicate after 5 minutes of rest in the sitting position) (Section 6.66.5)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titer
 - C3
 - AECA
 - RNAseq
 - Urine IgG
 - *Immune phenotyping*

Section 7.17 Follow-up Day 84

On Day 84 (\pm 5 days), subjects are to return to the clinic and the following procedures are to be performed:

- Complete physical exam (Section 6.3)
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- Serum tetanus antibody and VZV antibody testing if required. See Section 6.7.3 for additional information.
- *Immunogenicity sample collection (Section 6.7)*

Syntimmune, Inc. Page 10 of 18 12 April 2017

- PDAI Score (Section 6.4)
- *PD sample collection (Section 6.7)*
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titer
 - C3
 - AECA
 - RNAseq
 - Urine IgG
- Optional skin biopsy (Section 6.12)
- Photography (Section 6.11)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

Section 7.18 Follow-up Day 112 (End-of-Study) or Early Termination Visit

On Day 112 (\pm 5 days), subjects are to return to the clinic and the following procedures are to be performed:

- Complete physical exam (Section 6.3)
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- Pregnancy test (Section 6.7)
- Serum tetanus antibody and VZV antibody testing if required. See Section 6.7.3 for additional information.
- *Immunogenicity sample collection (Section 6.7)*
- PDAI Score (Section 6.4)
- *PD sample collection (Section 6.7)*
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titer
 - C3
 - AECA
 - RNAseq
 - Urine IgG
- Photography (Section 6.11)
- Concomitant medication assessment (Section 6.9)

• AE assessment (Section 6.10)

Section 7.16 Extended Follow-up Visits

• Extended follow-up visits will occur only if additional testing for anti-tetanus and/or anti-VZV titers are required. These visits will occur as needed at approximately 2 months post last dose and 3 months post last dose. See Section 6.7.3.

SECTION 8 REMOVING SUBJECTS FROM STUDY

Section 8.3 Replacements

Subjects withdrawn for a reason other than an AE will be replaced if they have not been
dosed or have only received 1 dose of study drug at the time of discontinuation, up to one
subject per cohort. Subjects who do not receive all doses of study drug will continue to be
followed through all scheduled study visits28 days after their last dose.

Section 8.4.1 Dose-Escalation Stopping Rule

• Dose escalation decisions will be made by a Dose Escalation Committee (DEC) and will be based on safety and pharmacodynamic evaluations including but not limited to, dose-limiting toxicities, AEs, SAEs, and total IgG levels.

Dose-limiting toxicity (DLT) will be defined generally as elinically significant, severe (Grade 3) AEs occurring in ≥ 2 subjects that are determined to be clinically significant and considered related to study drug.

If 2 or more subjects at any time in any cohort (8 total subjects per cohort) have Grade 3 AEs that are determined to be clinically significant and considered to be related to study drug, dosing will be halted within that cohort and no further dose-escalation to a higher dose will not occur. If the dose-escalation stopping rule is met in during cohort 1 (10 mg/kg) all safety data and all available pharmacodynamics will be reviewed and the cohort may resume (if applicable) or a new a cohort may be added at a dose at least 50% lower than the 10 mg/kg dose. If the stopping rule is not met in after Cohort 1, dose-escalation may proceed up to a maximum of 30 mg/kg. If the dose-escalation stopping rule is met in for the first time during Cohort 2, all safety data and all available pharmacodynamics will be reviewed and the cohort may resume (if applicable) or a new a cohort may be added at a dose a minimum of 30% lower than the Cohort 2 dose. If the stopping rule is not met in after Cohort 2, dose-escalation may proceed up to a maximum of 45 mg/kg; however, this cohort may also receive a dose equal to or less than 30 mg/kg based on evaluation of all safety and pharmacodynamic data.

Section 8.4.3 Individual Stopping Rule

• Dosing for any individual subject will be discontinued (i.e., no further study drug will be given to that subject) if the subject experiences any study drug-related SAE or any study drug-related non-SAE adverse event that, in the judgement of the Investigator and (following consultation with the Medical Monitor, if desired) suggest that it could be unsafe to administer further study drug to that subject. Additionally, a subject may will be discontinued from further treatment with study drug, at the discretion of the Investigator with consultation with the Medical Monitor, if they require a significant increase in dose(s) of anti-pemphigus medication(s) for the management of pemphigus

SECTION 9 STUDY DRUG

Section 9.6 Warnings and Precautions

• **Note:** Subjects must not receive any vaccinations from within 2 weeks of screening until 2 months after the last dose of study drug Day 56.

Section 9.6.2 Potential Immune Effects

- An antibody blocking FcRn is anticipated to have several effects. These include acceleration of catabolism of IgG, but not other immunoglobulin isotypes such as IgA and IgM, leading to dose-dependent decreases in circulating IgG levels by up to an estimated 50% from the baseline levels after a single dose and further decreases after multiple doses up to a 70%-80% reduction. Based on studies in humans, it is expected that with a single dose, the nadir of this effect will occur approximately 5 days after dosing. The time course of recovery of IgG following dosing in the Phase 1a study suggests that a return to within 30% of baseline levels observed at pretreatment normal limits-occurs within 4 weeks after a single dose and within 4 weeks after multiple doses as shown in NHPs.
- Given the normal adult range of total IgG of 700500-1600 mg/dL (Agarwal and Cunningham-Rundles, 2007; Furst, 2009; Gonzalez-Quintela et al, 2008; Joliff et al, 1982; Keystone et al, 2007; McMillan et al, 1997; van Vollenhoven et al, 2013in some references), with a mean of 1150 mg/dL, a 50% decrease in the mean would be to 575 mg/dL and a 50% decrease from the low end of the normal range used for the inclusion criteria of 700600 mg/dL in this study would be to 350300 mg/dL. An 80% decrease from baseline after multiple doses would result in IgG levels of 230 mg/dL and 140120 mg/dL, respectively. While these levels are in the range found in patients with primary humoral immunodeficiency [Ameratunga 2013], the levels will be transient. Further, in other conditions, the temporary (ie, less than 4 months) depletion of IgG (up to 95% reduction of total IgG as seen with immunoadsorption) does not appear to impart an increased risk of infection (Eming, 2006; Furst, 2009; Keystone et al, 2007; Schmaldienst et al, 2001; van Vollenhoven et al, 2013). Study subjects will be monitored clinically for any infection. Further, commercial IVIG can be given to reverse the low IgG levels in case of a bacterial infection occurring while their IgG levels are decreased.

SECTION 10 CONCOMITANT MEDICATION AND TREATMENT

- Any medications a subject receives within 14 days prior to enrollment through the end of study (Day 56) will be documented. Concomitant medication and treatment for co-existing conditions, including those for pemphigus, are permitted if not excluded below. Topical antibiotics are permitted to treat active infections that occur on study. Topical or systemic treatments for oral candidiasis are permitted. Topical lidocaine for transient pain relief is acceptable as needed. Significant increases in anti-pemphigus medications maywill result in subjects being discontinued from the study. Concomitant treatment that is medically indicated for any AEs the subject experiences during the study are permitted.
- Use of the following treatments will not be permitted during the study unless otherwise specified:
 - Rituximab or other anti-CD20 antibody
 - Monoclonal antibodies other than study drug
 - Any immunosuppressive drugs apart from corticosteroids, azathioprine, mycophenolate mofetil, or cyclosporine.
 - Topical steroids
 - Any dietary herbal supplements
 - Any investigational drug or device
 - Any vaccinations through Day 56. Following Day 56, subjects may be vaccinated at the discretion of the Investigator.

SECTION 11 SAFETY

Section 11.2 Adverse Event Definition

 For data collection, all untoward events that occur after informed consent through the last study visit 28 days after study drug dosing are to be recorded on eCRFs by the investigational site

Section 11.3.1 Serious Adverse Events

• <u>Death:</u> This includes any death that occurs while the subject is "on study" through the last study visit as well as any death that occurs within 28 days after study drug administration

Section 11.3.9.2 Time Frame for Reporting

Any death, SAE, pregnancy, or unexpected (and severe) AE experienced by the subject
after informed consent through the last study visit or within 28 days of receiving study
drug, regardless of relationship to study drug, or any death that occurs more than 28 days
after receiving study drug, and is believed to be study drug related, must be promptly
reported (within 24 hours of the Investigator becoming aware of the event) by telephone
or electronic transmission to the sponsor (or designee)

Section 11.3.9.3 Information to be Provided by the Investigator

SAEs must be recorded on the SAE form in the EDC system. This requirement includes
all SAEs that occur after informed consent through the last study visit and through
28 days after study drug dosing, and in addition, any SAE that are assessed as related to
study treatment by the Investigator, even if the SAE occurs more than 28 days after study
drug dosing.

Section 11.4.3 Follow-up of Adverse Events

• Any SAE or AE assessed as related to study drug that led to treatment discontinuation (including clinically significant abnormal laboratory values that meet these criteria) and ongoing 28 days after study drug dosing must be followed until either resolution of the event or determination by the Investigator that the event has become stable or irreversible. This follow up guidance also applies to related SAE that occur more than 28 days after study drug dosing. The status of all other continuing AEs will be documented as of 28 days after study drug dosing. The Investigator will follow all subjects who experience drug related AEs until there is a return to the subject's baseline condition, or until a clinically satisfactory resolution has been achieved. The appropriate follow-up visits must be scheduled and the specific tests repeated or performed as necessary. The status of all AEs will be documented as of the last study visit.

REFERENCES – The following were added:

Agarwal S and Cunningham-Rundles C. Assessment and clinical interpretation of reduced IgG values. Ann Allergy Asthma Immunol. 2007;99:281-283.

Eming R, Hertl M. Immunoadsorption in pemphigus. Autoimmunity. 2006;39:609-616.

Furst DE. Serum immunoglobulins and risk of infection: how low can you go? Semin Arthritis Rheum. 2009;39:18-29.

Gonzalez-Quintela A, Alende R, Gude R, Campos J, Rey J, Meijide LM, Fernandez-Merino C, Vidal C. Serum levels of immunoglobulins (IgG, IgA, IgM) in a general adult population and their relationship with alcohol consumption, smoking, and common metabolic abnormalities. Clin Exp Immunol. 2008:151:42-50.

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Joliff CR, Cost KM, Stivrins PC, Grossman PP, Nolte CR, Franco SM, et al. Reference intervals for serum IgG, IgA, IgM, C3 and C4 as determined by rate nephelometry. Clin Chem. 1982;28:126-128.

Keystone E, Fleischmann R, Emery P, Furst DE, van Vollenhoven R, Bathon J, et al. Safety and efficacy of additional courses of rituximab in patients with active rheumatoid arthritis: an open-label extension analysis. Arthritis Rheum. 2007;56:3896-3908.

McMillan SA, Douglas JP, Archbold GPR, McCrum EE, Evans AE. Effect of low to moderate levels of smoking and alcohol consumption on serum immunoglobulin concentrations. J Clin Pathol. 1997;50:819-822.

Schmaldienst S, Müllner M, Goldammer A, Spitzauer S, Banyai S, Hörl WH, Derfler K. Intravenous immunoglobulin application following immunoadsorption: benefit or risk in patients with autoimmune disease? Rheumatology. 2001;40:513-521.

van Vollenhoven RF, Emery P, Bingham CO 3rd, Keystone EC, Fleischmann RM, Furst DE, et al. Long-term safety of rituximab in rheumatoid arthritis: 9.5-year follow-up of the global clinical trial programme with a focus on adverse events of interest in RA patients. Ann Rheum Dis. 2013;72:1496-502.

SYNTIMMUNE

10-May-2017

Protocol Number:

SYNT001-103

IND Number:

132727

Study Drug:

SYNT001

Protocol Version, Date:

2.0, 12-April-2017

Clarification Letter Version:

1.0

Subject:

Buccal swab for DNA testing

To Whom It May Concern:

The purpose of this letter is to clarify any question as to the method used for the collection of a subject sample to evaluate a FcGR2A SNP (single nucleotide polymorphism) from clinical protocol SYNT001-103, titled "A Phase 1b, Multicenter, Open-Label, Safety, Tolerability, and Activity Study of SYNT001 in Subjects with Chronic Pemphigus (Vulgaris or Foliaceus)." The protocol includes an exploratory objective to evaluate FcGR2a SNP as an exploratory biomarker. This objective will be evaluated through the collection of a single buccal swab, from which DNA will be extracted and analyzed. This buccal swab will be collected from the subject prior to dosing on the day of first dose of SYNT001.

The protocol does not specify the collection will be made via buccal swab; however, the laboratory manual provides detailed instructions to the site on the collection materials and methods to be used. Subjects are informed of the assessment and the means by which it will be collected and data generated from it in the Informed Consent Form. In the event that there is a future protocol amendment, this clarification will be incorporated.

Sincerely.	טאי	
Syntimmune	Inc	

257 Park Ave S, 15th Floor, New York, New York, 10010

SYNTIMMUNE

11-Aug-2017

Protocol Number: SYNT001-103

Protocol Name: A Phase 1b, Multicenter, Open-Label, Safety, Tolerability, and

Activity Study of SYNT001 in Subjects with Chronic Pemphigus

(Vulgaris or Foliaceus)

IND Number: 132727

Study Drug: SYNT001

Protocol Version, Date: 2.0, 12-April-2017

Clarification Letter Version: 2.0

Subjects: Infusion Reactions

Concomitant Medications and Treatments

Adverse Event Reporting

The purpose of this memo is to present planned revisions and required corrections in the protocol text resulting from requests for clarification from Investigators. Text regarding management of infusion reactions has been revised. Text regarding pre-medications has been added and text regarding adverse events that require reporting within 24 hours has been corrected. Deleted text is crossed through and new text is in italics.

This text will be formally revised in the next forthcoming protocol amendment. In the interim please provide this correspondence to your Institutional Review Board as per local policy.

Section 9.6.1 (page 63)

<u>Current Text:</u> Management of Grade 1 infusion reactions include decreasing the rate of infusion by 50% and observing. Symptoms may also be treated as needed with medications such as diphenhydramine, hydrocortisone or acetaminophen.

<u>Revised text:</u> Management of Grade 1 infusion reactions include *interrupting the infusion or* decreasing the rate of infusion by 50% and observing. Symptoms may also be treated as needed with medications such as diphenhydramine, hydrocortisone or and acetaminophen, either alone or in combination, depending on the subject's signs and symptoms. If the infusion is interrupted

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or the infusion rate is decreased, it is important to note that all study drug infusions must be completed within 4 (four) hours of SYNT001 preparation.

<u>Rationale:</u> Provides clarification for the management of a Grade 1 infusion reaction. Provides a maximum duration of infusion in accordance with the requirements for SYNT001 preparation and administration outlined in the pharmacy manual.

Figure 1 (page 64)

Title:

Current text: Management of Mild (Grade 1) to Moderate (Grade 2) Infusion Reactions

Revised Text: Management of Mild (Grade 1) to Moderate (Grade 2) Infusion Reactions

<u>Rationale</u>: To be consistent with prior section regarding management of a Grade 1 infusion reaction and with CTCAE v4.03 definition of a Grade 1 infusion reaction.

Last Box:

<u>Current text:</u> Consider pre-medicating the subject with the same medication(s) 20-30 minutes in advance of subsequent administrations of SYNT001 and starting infusion at 50% of the planned infusion rate for the first 30 minutes, then returning to the intended infusion rate in the absence of any infusion reaction

Revised Text: Consider pre-medicating the subject with the same medication(s) 20-30 minutes in advance of subsequent administrations of SYNT001 and starting infusion at 50% of the planned infusion rate for the first 30 minutes, then returning to the intended infusion rate in the absence of any infusion reaction. If the infusion is interrupted or the infusion rate is decreased, it is important to note that all study drug infusions must be completed within 4 hours of SYNT001 preparation.

<u>Rationale</u>: Provision of a maximum duration of infusion in accordance with the requirements for SYNT001 preparation and administration as outlined in the pharmacy manual.

Section 10 (page 69)

<u>Current text:</u> All treatments a subject receives within 14 days prior to enrollment through the end of the study will be documented. Concomitant medication and treatment for co-existing conditions, including those for pemphigus, are permitted if not excluded below. Topical antibiotics are permitted to treat active infections that occur on study. Topical or systemic treatments for oral candidiasis are permitted. Topical lidocaine for transient pain relief is acceptable as needed. Significant increases in anti-pemphigus medications will result in subjects being discontinued from the study. Concomitant treatment that is medically indicated for any AEs the subject experiences during the study are permitted.

Revised text: All treatments a subject receives within 14 days prior to enrollment through the end of the study will be documented. Concomitant medications and treatments for co-existing conditions, including those for pemphigus, are permitted if not excluded below. Topical antibiotics are permitted to treat active infections that occur on study. Topical or systemic treatments for oral candidiasis are permitted. Topical lidocaine for transient pain relief is acceptable as needed. Significant increases in anti-pemphigus medications will result in subjects being discontinued from the study (See Section 8.4.3). Concomitant treatment that is medically indicated for any AEs the subject experiences during the study are permitted. Premedication is discouraged as prophylaxis against AEs or infusion reactions unless medically indicated from either past medical history, prior infusion reactions or AEs resulting from SYNT001 infusions.

Rationale: During recently conducted Site Initiation Visits for the Phase 1b studies of SYNT001, Syntimmune received questions about the possibility of infusion reactions with SYNT001. Indeed, infusion reactions are a common adverse effect of intravenous administration of monoclonal antibodies (mAb), even fully humanized mAbs. Infusion reactions are common with some FDA-approved mAbs, including anti-CD20 antibodies (Rituxan® [rituximab], Arzerra® [ofatumumab], Gazyva® [obinutumumab]), as well as with Cyramza® (ramucirumab) for gastric cancer, Darzelex® (daratumumab) for multiple myeloma, and Herceptin® (trastuzumab) for breast cancer. By contrast, infusion reactions are not reported in the package inserts for Soliris® (eculizumab) for paroxysmal nocturnal hemoglobinuria or Yervoy® (ipilimumab) for metastatic melanoma. Infusion reactions most commonly occur with the first infusion and are often related to the rate of protein infusion. For mAbs with frequent infusion reactions, it is typically recommended that pre-medications, such as corticosteroids, acetaminophen and an antihistamine, are administered prior to infusion, especially with the first infusion. For mAbs without associated infusion reactions or with uncommon or mild infusion reactions, premedications are not typically recommended and patients' signs and symptoms are managed individually.

While experience with SYNT001 is limited at this point, it is worth noting that there were no occurrences of infusion reactions in the recently completed healthy volunteer phase 1a single-

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ascending dose study. In that study, infusions of SYNT001 were given over 1 hour at doses up to 30 mg/kg. No subject had their infusion interrupted or rate of infusion decreased. No subject received premedication prior to SYNT001 infusion.

While the phase 1a results for SYNT001 may not be indicative of what will be observed in future studies, Syntimmune does not currently believe that it is necessary or appropriate to administer pre-medications to patients who will be receiving SYNT001 at the same doses and same infusion rates as the healthy volunteers in the phase 1a study. Of course, sites must be prepared to manage infusion reactions from mild to severe during every infusion given in this study. Should an infusion reaction occur in any subject, their signs and symptoms should be managed as medically indicated, including the interruption of SYNT001 infusion or slowing of the rate of infusion. If frequent infusion reactions are observed in the phase 1b study, the issue of pre-medication will certainly be discussed with the investigators.

Section 11.3.9.2 (page 76)

Cincoroly

<u>Current text:</u> "Any death, SAE, pregnancy, or unexpected (and severe) AE experienced by the subject after informed consent through the last study visit, regardless of relationship to study drug, must be promptly reported (within 24 hours of the Investigator becoming aware of the event) by telephone or electronic transmission to the sponsor (or designee)."

Revised text: "Any death, SAE, or pregnancy, or unexpected (and severe) AE experienced by the subject after informed consent through the last study visit, regardless of relationship to study drug, must be promptly reported (within 24 hours of the Investigator becoming aware of the event) by telephone or electronic transmission to the sponsor (or designee)."

<u>Rationale</u>: To clarify, adverse (severe) events that are not considered SAEs do not need to be reported within 24 hours but reported per section 11.3.6.

Sincerely,			
PPD			
PPD			
Syntimmune, I	lnc.		

SYNTIMMUNE

21-Sep-2017

Protocol Number:

SYNT001-103

Protocol Name:

A Phase 1b, Multicenter, Open-Label, Safety, Tolerability, and

Activity Study of SYNT001 in Subjects with Chronic Pemphigus

(Vulgaris or Foliaceus)

IND Number:

132727

Study Drug:

SYNT001

Protocol Version, Date:

2.0, 12-April-2017

Clarification Letter Version: 3.0

Subjects:

Inclusion Criteria

The purpose of this memo is to present a planned revision ahead of the next forthcoming protocol amendment. In the interim, please provide this correspondence to your Institutional Review Board as per local policy and request expedited review and approval.

Section 5.2 Inclusion Criteria #5 (page 35)

Current Text: Body mass index (BMI) 18.5 - 35.0 kg/m²

Revised text: Body mass index (BMI) 18.5 - 39.9 kg/m²

Rationale: Patients who may be otherwise eligible to participate in the study are excluded due to BMI. We would like to be able to offer these individuals the opportunity to participate.

Syntimmune, Inc.

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Syntimmune, Inc.

CLINICAL STUDY PROTOCOL

A Phase 1b, Multicenter, Open-Label, Safety, Tolerability, and Activity Study of SYNT001 in Subjects with Chronic Pemphigus (Vulgaris or Foliaceus)

Protocol Number: SYNT001-103

IND Number: 132727

Study Drug: SYNT001

Sponsor: Syntimmune, Inc.

257 Park Avenue South

15th Floor

New York, NY 10010

Medical Monitor:

Wallace House

17-21 Maxwell Place Stirling, Scotland FK81JU

Mobile Phone: PPD

Office Phone: PPD

ext. PPD

Original Protocol: 18 January 2017
Amendment 1.1: 21 March 2017
Amendment 2.0: 12 April 2017
Amendment 3.0: 10 October 2017

Confidentiality Statement

The information contained herein is confidential and the proprietary property of Syntimmune, Inc. and any unauthorized use or disclosure of such information without the prior written authorization of Syntimmune is expressly prohibited.

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SPONSOR SIGNATURE

I have read and approve this protocol. My signature, in conjunction with the signature of the Investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonisation Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), and the ethical principles that have their origins in the Declaration of Helsinki.

	10-10-2017
PPD	Date of Signature
	(DD Mm YYYY)

PROCEDURES IN CASE OF EMERGENCY

Serious Adverse Events

Any death or serious adverse event (SAE)* occurring in a subject while receiving study drug or within 7 days of receiving study drug, even though the event may not appear to be study drug related, must be promptly reported (within 24 hours) by telephone or electronic communication to the sponsor (or designee).

Emergency Contact Information

For SAE reporting:	For any other questions or to contact the Medical Monitor:
Medpace Clinical Safety	PPD Mobile phone: PPD
Medpace SAE hotline: Telephone: PPD dial p or PPD	PPD Mobile phone: PPD
PPD dial P	Office phone: PPD ext.
Facsimile: PPD or PPD e-mail: PPD	PPD
	•

SAE CRITERIA

- * A <u>serious adverse event</u> (SAE) is any untoward medical occurrence that at any dose results in any of the following outcomes, regardless of relationship to study drug (see <u>Section 11.3.1</u>, Serious Adverse Events for additional information):
 - Death
 - Life-threatening adverse drug event
 - Inpatient hospitalization or prolongation of existing hospitalization
 - A persistent or significant disability/ incapacity
 - A congenital anomaly/birth defect
 - An important medical event that may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Syntimmune, Inc.

Page 3 of 100
Confidential and Proprietary

Amendment 3.0 Final 10October

INVESTIGATOR SIGNATURE

I have read and approve this protocol. My signature, in conjunction with the signature of the sponsor, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonization Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), and the ethical principles that have their origins in the Declaration of Helsinki.

Nothing in this document is intended to limit the authority of a physician to provide emergency

medical care under applicable regulations.		
Investigator Signature	Date of Signature (DD Mm YYYY)	
Name of Investigator (please print)		

1 SYNOPSIS

Study title	A Phase 1b, Multicenter, Open-Label, Safety, Tolerability, and Activity Study of SYNT001 in Subjects with Chronic Pemphigus (Vulgaris or Foliaceus)
Protocol number	SYNT001-103
Number of study centers	Approximately 10 (US)
Clinical phase	Phase 1b
Study background	SYNT001, a humanized, affinity-matured IgG4-kappa monoclonal antibody (mAb), blocks IgG and IgG immune complex (IC) interactions with the neonatal Fc receptor (FcRn) and thereby the major functions of FcRn in protecting IgG and IgG immune complexes from degradation and their role in downstream signaling events. Specific and high affinity blockade of FcRn with SYNT001 has been shown to increase the catabolism of IgG and IgG IC in healthy volunteers. This predicts that SYNT001 will also accelerate degradation of endogenous circulating IgG autoantibodies and IgG-antigen IC specifically involved in the pathogenesis of autoimmunity. Blocking FcRn interactions with IgG containing immune complexes further predicts that SYNT001 will have consequences for innate and adaptive cellular immunity. In the first instance, blocking multimeric IgG IC interactions with FcRn within antigen presenting cells will result in inhibition of IC-stimulated inflammatory cytokine production and release by these cells. In addition, as FcRn determines the intracellular itinerary of IgG immune complexes within and among compartments important in cellular immunity, it is further anticipated that SYNT001 will block antigen processing and presentation of antigens contained within IC that otherwise lead to CD8 ⁺ and CD4 ⁺ T cell activation. Thus, SYNT001 will specifically target immune functions associated with IgG and IC that are involved in many autoimmune conditions and dismantle their ability to cause disease. SYNT001 targets mechanisms contributing to pathology in a variety of IgG-mediated autoimmune disorders, including warm antibody autoimmune hemolytic anemia (WAIHA), pemphigus, and chronic inflammatory demyelinating polyneuropathy (CIDP). While current treatments for certain autoimmune disorders including chronic steroids, immunosuppressants, intravenous immunoglobulin (IVIG), plasmapheresis, and anti-CD20 monoclonal antibodies (mAbs), such as rituximab, can be effective, they are frequently associated with significant
	adverse effects, and delayed or non-durable responses. Pemphigus is a rare group of blistering autoimmune diseases that affect the skin and mucous membranes. Autoantibodies are thought to play an important

	pathogenic role in the mucosal and cutaneous manifestations in patients with pemphigus. Administration of SYNT001, leading to a significant decrease in total IgG, and thereby a corresponding decrease in the level of the pathogenic autoantibodies as well as the ICs to which they are associated, should lead to a decrease in the mucosal and cutaneous manifestations in subjects with pemphigus. Moreover, the ability of SYNT001 to reduce circulating immune complexes (CICs) and the associated innate and adaptive immune responses may allow for further sustained disease modification.	
Study rationale	This study is being conducted to further evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity of intravenous (IV) SYNT001 as well as its effects on pemphigus disease activity markers.	
Study objectives	Primary objective	
	To evaluate the safety and tolerability of 5 once-weekly IV infusions of SYNT001 at different dose levels in subjects with chronic pemphigus (vulgaris or foliaceus)	
	Secondary objectives	
	To determine the PK of SYNT001 following 5 once-weekly 1-hour IV infusions at different dose levels	
	To assess the effect of 5 once-weekly doses of SYNT001 at different dose levels on the following PD biomarkers: Output Description: Output Descri	
	 Immunoglobulins: IgG, IgG subtypes (IgG1-4), IgA, IgM Albumin 	
	To assess the effect of 5 once-weekly doses of SYNT001 at different dose levels on the following disease activity markers:	
	o Serum anti-desmoglein (Dsg) (1 and 3) antibody levels	
	o Pemphigus Disease Area Index (PDAI)	
	To assess immunogenicity (anti-SYNT001 antibodies)	
	Exploratory objectives	
	To assess the effect of 5 once-weekly doses of SYNT001 at different dose levels on the following biomarkers, including:	
	 Serum anti-epithelial cell antibody (AECA) levels by indirect immunofluorescence 	
	Circulating immune complexes (CIC)	
	o Complement component 3 (C3)	
	 Exploratory biomarkers (FCGR2A (single nucleotide polymorphism- SNP), RNAseq, urine IgG) 	

0	Immune phenotyping by flow cytometry for CD3 ⁺ CD4 ⁺ T,
	CD3 ⁺ CD8 ⁺ T, monocytes, NK cells and B cells

- SYNT001 levels in skin biopsies (optional)
- Exploratory biomarkers to investigate immune response associated with pemphigus
- To characterize corticosteroid use during the study

Study design

Phase 1b, multicenter, open-label, safety, tolerability, and activity study

Methodology

Two cohorts of 8 eligible subjects each will receive 5 once-weekly 60-minute infusions of SYNT001 in planned doses of 10 mg/kg or 30 mg/kg. Based on review of safety, PD, and clinical outcomes of these 2 cohorts, a third cohort of up to 8 subjects may be treated at another dose, with a maximum dose of 45 mg/kg, but may also be lower than 10 mg/kg or between 10 and 30 mg/kg, inclusive.

Cohort	No. of subjects	Dose
1	8	SYNT001 10 mg/kg
2	8	SYNT001 30 mg/kg

Cohorts will be dosed sequentially beginning with Cohort 1. The first 2 subjects will be dosed at least 24 hours apart. A review of the 24-hour safety data for the first subject will be performed to ensure that there are no overt safety concerns before dosing the second subject. A review of the 7-day safety data for the first 2 subjects will be performed prior to dosing the remaining 6 subjects in the cohort. This evaluation will include a review of AE/SAE reports, vital sign assessments, physical examinations, ECGs, and clinical laboratory testing. The seriousness, severity, and relatedness of AEs/SAEs will also be considered in the safety evaluation. Safety data will be reviewed on a continuous basis throughout the study. All safety data and any available and relevant PD data through Day 42 (2 weeks after the last subject's last dose in Cohort 1) will be reviewed by a dose escalation committee before Cohort 2 is initiated. Escalation to Cohort 2 will proceed if there are no concerning safety signals and the review of available and relevant PD data supports advancing to a higher dose. The dose for Cohort 2 will be finalized after review of the safety and PD data, but will not exceed 30 mg/kg. Cohort 2 and Cohort 3, if added, will be dosed per the same schedule as Cohort 1.

On days where study drug is administered, vital sign and pulse oximetry measurements will be collected immediately prior to the infusion; 15, 30, and 45 minutes after the start of the infusion; at completion of the infusion; and 30 minutes, 1 hour and 2 hours following completion of the infusion.

On Days 0 and 28, PK blood samples will be collected prior to infusion start and then over the subsequent 48 hours. Subjects will remain at the clinic through the

6-hour PK sample collection and will return to the clinic for the 24- and 48-hour collections. Additional samples will be collected on Days 5 and 33. On Day 0 photographs will be taken of active lesions. Follow-up photographs will be taken of the same areas on Days 33, 56, 84 and 112. If a subject begins a steroid taper, additional photographs will be taken at the clinic visit during which the decision to begin the taper is made. Subsequent visits will occur on Days 1, 2, 5, 7, 12, 14, 19, 21, 28, 29, 30, 33, 42 and 56 for safety assessments, study drug dosing, sample collections, and other study procedures. Subjects will return to the clinic on Days 84 and 112 for follow-up visits. Subjects whose total IgG is not within 30% of their Day 0 baseline value and not above 500 mg/dL at the Day 112 visit will be referred for further management. See Table 1 for a schedule of all study events. To assess safety and tolerability, subjects will undergo physical examinations (PEs; including weight), vital sign measurements, clinical (safety) laboratory tests, adverse event (AE) assessments, concomitant medication assessments, and electrocardiograms (ECG). Approximately 16; two cohorts of 8 subjects each. An additional cohort of up to **Number of subjects** 8 subjects may be enrolled. Subjects who withdraw for any reason other than an AE and who do not receive study drug or have only received one dose of study drug may be replaced, up to one subject per cohort. The maximum number of subjects who may be enrolled in this study is 27 (24 + up to 3 replacements, as necessary). Within each dosing cohort, no more than 3 subjects with pemphigus foliaceus may be enrolled. Diagnosis and main **Inclusion criteria:** entry criteria Subjects must meet the following criteria to be included: 1. Willing and able to read, understand and sign an informed consent form; 2. Male or female \geq 18 years of age at the time of screening; 3. Documented diagnosis of pemphigus vulgaris or foliaceus based on all 3 of the following criteria: a. Documented clinical history consistent with pemphigus vulgaris or foliaceus (clinical presentation defined as mucosal and/ or skin lesions): b. Presence of Anti-Dsg 1 or 3 antibodies above the upper limit of normal; c. History of at least one positive tissue-based test (e.g., biopsy, direct immunofluorescence [DIF]) 4. Active disease: Lesions lasting > 2 weeks, and 3 active lesions in skin or mucosa or 2 active lesions with at least one being a skin lesion > 1 cm diameter:

- a. If treated with rituximab or other anti-CD20 antibodies, last dose
 12 months prior to screening;
- b. If being treated with other immunosuppressants (i.e., azathioprine, mycophenolate mofetil or cyclosporine), must be on stable dose (< 10% change in dose) for 6 weeks prior to screening;
- c. If being treated with corticosteroids, must be ≤ 1mg/kg/day of prednisone or equivalent and stable (< 10% change in dose) for 2 weeks prior to screening;
- d. Allowed topical therapies for pemphigus lesions upon entering the study include petroleum jelly or Aquaphor® for the skin or chlorhexidine for the mouth
- 5. Body mass index (BMI) $18.5 39.0 \text{ kg/m}^2$;
- 6. Has a negative pregnancy test (for women of childbearing potential) documented prior to the first dose of study drug;
- 7. Females of childbearing potential must agree to be abstinent or else use any two of the following medically acceptable forms of contraception (<1% per year failure rate) from the Screening Period through the final study visit: oral contraceptive, condom with or without spermicidal jelly, diaphragm or cervical cap with spermicidal jelly, or intra-uterine device (IUD). A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception.
- 8. Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months do not require contraception during the study.
- 9. Males with female partners of childbearing potential, including males who are surgically sterile (post vasectomy), must agree to be abstinent or else use a medically acceptable form of contraception from the screening period through the final study visit.

Exclusion criteria:

Subjects meeting any of the following criteria are to be excluded:

- 1. Subject unable or unwilling to comply with the protocol;
- 2. Active non-hematologic malignancy or history of non-hematologic malignancy in the 3 years prior to screening (exclusive of non-melanoma skin cancer and cervical cancer in situ);
- 3. Positive for HIV or hepatitis C antibody;
- 4. Positive for hepatitis B surface antigen;
- 5. Active infection or history of recurrent infections;
- 6. IVIG use within 60 days of screening;
- 7. Received any cytotoxic (other than azathioprine) or mAb therapy in the 3 months prior to screening;

	 Any exposure to an investigational drug or device within the 30 days prior to screening Plasmapheresis or immunoadsorption within 60 days of screening Cellular therapy, including CAR-T, at any time prior to screening Use of any immunosuppressive drugs apart from corticosteroids, azathioprine, mycophenolate mofetil, or cyclosporine within 3 months of screening Serum total IgG < 600 mg/dL; Subject has any current medical condition that, in the opinion of the Investigator, may compromise their safety or compliance, preclude successful conduct of the study, or interfere with interpretation of the results (e.g., a significant pre-existing illness or other major comorbidity that the Investigator considers may confound the interpretation of the study results); Any vaccination within 2 weeks of screening
Study drug, dosage,	SYNT001
and administration	Doses: 10 mg/kg and 30 mg/kg. A third cohort of up to 8 subjects may be treated at another dose, with a maximum dose of 45 mg/kg, but may also be lower than 10 mg/kg or between 10 and 30 mg/kg, inclusive.
	SYNT001 is provided as a liquid at a nominal concentration of 50 mg/mL. SYNT001 is diluted in Dextrose 5% in Water (D5W) to prepare the solution for infusion.
	Route of administration: IV in 250 mL over 1 hour
Control, dose, and route of administration	Not applicable
Duration of subject participation and duration of study	Up to 126 days (18 weeks): Screening of up to 2 weeks (14 days); Treatment period of 8 weeks (56 days); Follow-up period of 8 weeks (56 days)

Prohibited Concomitant treatments

All treatments a subject receives within 14 days prior to enrollment through the end of the study will be documented. Concomitant medication and treatment for co-existing conditions, including those for pemphigus, are permitted if not excluded below. Topical antibiotics are permitted to treat active infections that occur on study. Topical or systemic treatments for oral candidiasis are permitted. Topical lidocaine for transient pain relief is acceptable as needed. Significant increases in anti-pemphigus medications will result in subjects being discontinued from the study. Concomitant treatment that is medically indicated for any AEs the subject experiences during the study are permitted. Premedication is discouraged as prophylaxis against AEs or infusion reactions unless medically indicated from either past medical history, prior infusion reactions or AEs resulting from SYNT001 infusions.

Use of the following medications will not be permitted during the study unless otherwise specified:

- Rituximab or other anti-CD20 antibody
- Monoclonal antibodies other than study drug
- Any immunosuppressive drugs apart from corticosteroids, azathioprine, mycophenolate mofetil, or cyclosporine
- Topical steroids
- Any dietary herbal supplements
- Any investigational drug or device
- Any vaccinations through Day 56. Following Day 56, subjects may receive vaccinations at the discretion of the Investigator.

If over a period of at least two weeks on study drug, a subject on corticosteroids shows the absence of new lesions and significant healing of lesions that existed at study baseline, a slow corticosteroid taper may be started as per the following suggested schedule

- If on > 30 mg of prednisone per day, decrease by 10 mg every two weeks until a dose of 30 mg per day then decrease by 5 mg every two weeks
- If on < 30 mg of prednisone per day, decrease by 5 mg every two weeks

Safety assessments

Safety assessments include AEs, serious adverse events (SAEs), PEs, vital sign measurements, clinical safety laboratory evaluations, ECGs, and reasons for treatment discontinuations due to toxicity. Safety assessments will be performed at specified time points and prior to discharge from the clinic. Vital sign measurements, including blood pressure, pulse rate, respiratory rate, and temperature will be monitored throughout the study. Pulse oximetry will be monitored during the study drug infusion and for 2 hours following the end of the infusion.

	The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; Version 4.03) will be used for grading clinical and laboratory AEs. The AE reporting period for a subject enrolled in the study begins when the subject provides informed consent and is continued through the last study visit. All AEs that occur in the enrolled subjects during the AE reporting period must be recorded, regardless of the relationship of the AE to study drug. Any known untoward event that occurs beyond the AE reporting period that the Investigator assesses as related to study drug should also be recorded.
Dose-escalation rules	Dose escalation decisions will be made by a Dose Escalation Committee (DEC) and will be based on safety and pharmacodynamic evaluations including but not limited to, dose-limiting toxicities, AEs, SAEs, and total IgG levels. Dose-limiting toxicity (DLT) will be defined generally as severe (Grade 3) AEs occurring in ≥ 2 subjects that are determined to be clinically significant and considered related to study drug. If 2 or more subjects at any time in any cohort (8 total subjects per cohort) have Grade 3 AEs that are determined to be clinically significant and considered to be related to study drug, dosing will be halted within that cohort and dose-escalation to a higher dose will not occur. If the dose-escalation stopping rule is met during Cohort 1 (10 mg/kg) all safety data and all available pharmacodynamics data will be reviewed and the cohort may resume (if applicable) or a new cohort may be added, at a dose at least 50% lower than the 10 mg/kg dose. If the stopping rule is not met in Cohort 1 (10 mg/kg), dose-escalation may proceed up to a maximum of 30 mg/kg. If the dose-escalation stopping rule is met for the first time during Cohort 2, all safety data and all available pharmacodynamics data will be reviewed and the cohort may resume (if applicable) or a new cohort may be added at a dose at least 30% lower than the Cohort 2 dose. If the stopping rule is not met in Cohort 2, dose-escalation may proceed up to a maximum of 45 mg/kg; however, this cohort may also receive a dose equal to or less than 30 mg/kg based on evaluation of all safety and pharmacodynamic data.
Study stopping rule Individual stopping	If any subject experiences a life-threatening AE (Grade 4) that is considered to be related to study drug, any further dosing in all enrolled subjects will be suspended until the DEC has evaluated the event and determined the next appropriate course of action. At any time during the study, the study may be discontinued if the DEC determines that further drug exposure would pose an undue risk to subjects. Dosing for any individual subject will be discontinued (i.e., further treatment
rule	with the study drug will not be given) if the subject experiences any study drug-

	related SAE or any study drug-related non-SAE adverse event that, in the judgement of the Investigator (following consultation with the Medical Monitor, if desired) suggest that it could be unsafe to administer further study drug to that subject. Additionally, a subject will be discontinued from further treatment with study drug, at the discretion of the Investigator with consultation with the Medical Monitor, if they require a significant increase in dose(s) of antipemphigus medication(s) for the management of pemphigus.
Pharmacokinetics	The PK of SYNT001 will be evaluated following the first and last (fifth) doses of SYNT001.
	Starting on Days 0 and 28, serum samples will be collected just prior to the start of study drug infusion (pre-dose), at 5 minutes and 2, 4, 6, 24, and 48 hours after the end-of-study drug infusion. Additional samples will be collected on Days 5 and 33. Study drug concentration will be used to calculate the following PK parameters: $t_{1/2}$, C_{max} , T_{max} , AUC_{0-24} , and $AUC_{0-\infty}$.
Pharmacodynamics/ Activity	PD samples will be collected for analysis of IgG (serial assessment of IgG levels to identify C _{min} , T _{min}); IgG1-4 subtype levels; IgA levels; IgM levels; albumin levels; anti-Dsg (1 and 3) antibody levels; serum AECA by direct immunofluorescence; CIC; C3; exploratory biomarkers (<i>FCGR2A</i> SNP, RNAseq, urine IgG, CD3 ⁺ CD4 ⁺ T, CD3 ⁺ CD8 ⁺ T, monocytes, NK cells and B cells), and additional exploratory analyses to investigate immune response associated with pemphigus.
Immunogenicity	Samples will be collected for immunogenicity analyses on Days 0 (pre-dose), 14, 28, 56, 84 and 112.
Skin biopsy	Optional skin biopsy samples from lesional or non-lesional skin will be collected on Day 0 pre-dose and on Days 1, 2, 14, 33, 56 and 84 to analyze SYNT001 levels.
Photography	Photographs of active lesions will be taken at Day 0. Follow-up photographs of the same areas will be taken on Days 33, 56, 84 and 112. Subjects who begin a steroid taper will have additional photographs taken at the clinic visit during which the decision to begin the taper is made.
Statistical methods	Sample size consideration
	Formal sample size calculations were not performed. The number of subjects was chosen based on feasibility and was considered sufficient to meet the study objectives.
	Data presentations/Descriptive statistics
	Three populations will be employed in the analysis of study data.
	<u> </u>

- The intent-to-treat (ITT) population will consist of all subjects who have received at least one dose of study drug. All safety analyses will be performed on the ITT population.
- The PK population will consist of all subjects who receive at least one dose of study drug and have sufficient post-dose blood samples to obtain PK parameters.
- The PD population will consist of all subjects who receive at least one dose of study drug and have post-dose PD data available.

Primary safety analyses will be performed on the ITT population. Demographics, subject disposition, and screening and baseline characteristics will be summarized for the PK and ITT populations, where appropriate.

Criteria for evaluation

Objective	Endpoint
Primary	-
Safety and tolerability of 5 once- weekly IV infusions of SYNT001 to subjects with pemphigus vulgaris or foliaceus	AEs and clinical (safety) laboratory tests
Secondary	
PK of SYNT001 following a 1-hour IV infusion	$\begin{array}{c} PK \ parameters: t_{1/2}, C_{max}, T_{max}, \\ AUC_{0\text{-}24}, and AUC_{0\text{-}\infty}. \end{array}$
Effect of 5 once-weekly IV doses of SYNT001 on: • Total IgG (IgG1-4), IgA, IgM, and albumin • Serum anti-Dsg (1 and 3) antibodies	Changes in levels of IgG, IgG subtypes (IgG1-4), IgA, IgM, albumin, serum anti-Dsg (1 and 3) antibodies
Assess immunogenicity	Anti-SYNT001 antibodies
Disease Activity	PDAI Scores
Exploratory	
Effect of 5 once-weekly IV doses of SYNT001 on biomarkers including: • CIC • C3 • Serum anti-epithelial cell antibody (AECA) levels • Exploratory biomarkers (FCGR2A SNP, RNAseq, urine IgG) • Immune phenotyping by flow cytometry	Changes in CIC; C3; AECA levels by indirect immunofluorescence; <i>FCGR2A</i> SNP; RNAseq; urine IgG, CD3 ⁺ CD4 ⁺ T, CD3 ⁺ CD8 ⁺ T, monocytes, NK cells and B cells; urine IgG levels; changes in blood transcriptome

Exploratory biomarkers to investigate immune response associated with pemphigus	
Concomitant Treatment	Corticosteroid use during the study
SYNT001 levels in skin biopsies	Measures of SYNT001 levels in skin biopsies

Treatment-emergent AEs (TEAEs) will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA®; Version 19 or higher) System Organ Class (SOC) and preferred term, classified from verbatim terms. The incidence and percentage of subjects with at least 1 occurrence of a preferred term will be included, using the most severe grade. The number of events per preferred term will also be summarized. Causality (relationship to study treatment) will be summarized separately.

TEAEs, SAEs, and AEs leading to withdrawal, or treatment discontinuation will be listed by subject, and cohort using SOC and preferred terms. Duration of AEs will be determined and included in listings, along with action taken, and outcome.

Laboratory results will be summarized by time point and cohort. The incidence of laboratory abnormalities will be summarized. The worst on-study grade after the first dose of study drug will be summarized. Results for variables that are not coded will be presented in the listings as below, within, and above the normal limits of the central laboratory. Vital sign measurements will be summarized by cohort at each scheduled time point using descriptive statistics.

Study drug concentrations will be used to calculate the following PK parameters: $t_{1/2}$, C_{max} , T_{max} , and area under the curve (AUC). PK parameters will be determined using non-compartmental method(s). Descriptive statistics of PK parameters for SYNT001 will include mean, standard deviation (SD), coefficient of variation (CV), median, minimum, and maximum. T_{max} will be reported as median and range. All descriptive statistics will be performed on untransformed PK parameters and after log_{10} transformation of PK parameters.

PD results will be summarized by cohort. Descriptive statistics of PD parameters for SYNT001 will include mean, SD, CV, median, minimum, and maximum.

Immunogenicity results will be summarized by cohort. Descriptive statistics will include mean, SD, CV, median, minimum, and maximum.

Table 1: Study Assessments

	Screening		Treatment Period							F	Follow-Up							
Timepoint (Study Day)	-14 to -1	0	1 (±1 hr)	2 (± 2 hr)	5 ^p (±4 hr)	7 (±6 hr)	12 ^p (±6 hr)	14 (±6 hr)	19 ^p (±6 hr)	21 (±6 hr)	28 (±6 hr)	29 (±1 hr)	30 (±2 hr)	33 (±4 hr)	42 (±3 days)	56 (±5 days)	84 (±5 days)	112 (±5 days) or ET Visit
Informed Consent	X																	
Demographics/Medical History	X																	
Inclusion/Exclusion	X																	
Physical Examination ^a	X	X				X		X		X	X				X	X	X	X
Vital Signs ^b	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pulse Oximetry ^c		X				X		X		X	X							
Clinical Safety Labs ^d	X	X				X		X		X	X			X	X	X	X	X
Pregnancy test ^e	X	X														X		X
Hepatitis & HIV Screen	X																	
12-Lead ECG ^f	X	X					X				X					X		
Tetanus & VZV antibodies		X														X	X	X
PDAI Score		X				X		X		X	X			X	X	X	X	X
PK Sampling ^h		X	X	X	X						X	X	X	X				
Immunogenicity ⁱ		X						X			X					X	X	X
Study Drug Administration ^j		X				X		X		X	X							
Immunoglobulins (IgG, IgA, IgM) and IgG subtypes (IgG 1-4) ^k	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ^q
CIC		X			X	X	X	X	X	X	X			X	X	X	X	X
Anti-Dsg (1 & 3) antibody titer	X	X				X		X						X		X	X	X
C3 and AECA ¹		X						X						X		X	X	X
FCGR2A ^m by buccal swab		X																
RNAseq ^m		X						X						X		X	X	X
Urine IgG ^m		X						X						X		X	X	X
Immune phenotyping ⁿ		X									X					X		
Pemphigus immune response biomarkers		X			X	X	X	X	X	X	X			X	X	X	X	X
Optional Skin Biopsy		X	X	X				X						X		X	X	
Photography ^o		X												X		X	X	X
Adverse Events			To be collected from the date that the ICF is signed through the last study visit															
Concomitant Medications					To be	e collec	ted fron	n within	14 day	s prior	to Day	0 throu	gh the i	last study	visit			

ECG = electrocardiogram; ET= Early Termination; HIV = human immunodeficiency virus; ICF = informed consent form; PD = pharmacodynamic; PK = pharmacokinetic; VZV = varicella-zoster virus

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- a: Complete PE, including weight, to be performed. Height and BMI will be additional assessments conducted at screening.
- b: **Vital sign** measurements (sitting blood pressure, heart rate, respiratory rate, and oral temperature) to be obtained after 5 minutes of seated rest. Any abnormal measurements are to be repeated after 5 minutes of rest. On Days 0, 7, 14, 21, and 28 vital sign measurements will be collected immediately prior to the infusion; 15, 30, and 45 minutes after the start of the infusion; at completion of the infusion; and 30 minutes, 1 hour and 2 hours following completion of the infusion.
- c: **Pulse oximetry:** On Days 0, 7, 14, 21, and 28, pulse oximetry to be measured immediately prior to the infusion; 15, 30, and 45 minutes after the start of the infusion; at completion of the infusion; and 30 minutes, 1 hour and 2 hours following completion of the infusion.
- d: Clinical safety labs: hematology, clinical chemistry, and urinalysis (see Section 6.7 for a complete list). Full clinical safety lab draws will be collected at Screening and on Days 0, 7, 14, 21, 28, 33, 42, 56, 84 and 112.
- e: **Pregnancy test:** To be performed at time of screening and prior to first dose of SYNT001 on Day 0 and on Days 56 and 112 (urine or serum test is acceptable, however, positive urine tests must be confirmed with serum testing.)
- f: Digital 12-lead **ECG** to be obtained after 5 minutes of rest in the supine position and in triplicate at least 1-2 minutes apart (see Section 6.6 for additional information). On Days 0 and 28 to be obtained 5 minutes after the completion of infusion. Day 12 ECG will be collected only if the visit is conducted at the study site.
- g: **Serology**: Testing at Day 56 will not be done for any subject whose baseline titer is below the level of detection. If the Day 56 results are greater than 30% below the baseline value, or if the subject falls below the level of detection, the subject will be re-tested at Day 84; if still below the baseline value (or level of detection), the subject will be re-tested at Day 112. Any subject whose baseline value for tetanus or VZV was above the detectable level at baseline, and is not within 30% of the baseline value or is below the detectable level by Day 112, will be referred to their primary care physician for further management. See Section 6.7.3 for additional information.
- h: **PK:** Starting on Days 0 and 28, serum samples will be collected just prior to the start of study drug infusion (pre-dose), and at 5 minutes and 2, 4, 6, 24, and 48 hours after the end-of-study drug infusion. Additional samples will be collected on Days 5 and 33. See Section 6.7.4 for additional information.
- i: Immunogenicity: Blood samples will be collected pre-dose when collected on dosing days. Samples will be collected on Days 0, 14, 28, 56, 84 and 112. See Section 6.7.6 for additional information.
- j: Prior to **study drug infusion**, SYNT001 drug product is to be diluted in Dextrose 5% in Water (D5W) to a total volume of 250 mL and administered intravenously over 1 hour using a 0.2-micron, inline filter. See Section 9 for additional information.
- k: Immunoglobulins (IgG, IgA, IgM) and IgG subtypes (IgG 1-4): Collected for measurements of IgG, IgG subtypes (IgG1-4), IgA, and IgM at every visit. On Days 0, 7, 14, 21, and 28, samples are collected prior to infusion of study drug. See Section 6.7.5 for additional information
- 1: Exploratory PD samples (C3 and AECA): collected pre-dose when collected on dosing days. See Section 6.7.5 for complete information.
- m: Buccal samples to be collected and stored; pending review of clinical and pharmacodynamics assessments
- n: Immune phenotyping by flow cytometry for measurement of CD3⁺CD4⁺ T, CD3⁺CD8⁺ T, monocytes, NK cells and B cells
- o: Photographs of active lesions taken prior to first dose on Day 0. Follow-up photographs will be taken at Days 33, 56, 84 and 112. Subjects who begin a steroid taper will have additional photographs taken at the clinic visit during which the decision to begin the taper is made.
- p: Visit Days 5, 12 and 19 may be conducted via at-home nursing in lieu of a subject visit to the study site.
- q: Subjects will return to the clinic on Days 84 and 112 for follow-up visits. Subjects whose total IgG is not within 30% of their Day 0 baseline value and not above 500 mg/dL at the Day 112 visit will be referred for further management.

Table 2: Timing Window Allowances for PK/PD Sampling, ECG, and Vital Sign Measurements

Pharmacokinetic and Pharmacodynamic Sampling	
Timepoint	Tolerance Window
0 hour	−240 min to 0 hour
5 minutes post end-of-infusion	± 5 minutes
2, 4, & 6 hours post end-of-infusion	± 15 minutes
24 hours post end-of-infusion	\pm 60 minutes
48 hours post end-of-infusion	± 120 minutes
ECG	
Timepoint	Tolerance Window
5 minutes post end-of-infusion	± 10 minutes
Vital Signs ^a	
Timepoint	Tolerance Window
0 hour	−240 min to 0 hour
15, 30, and 45 minutes after start of infusion	± 5 minutes
60 minutes after start of infusion	± 10 minutes
30, 60 and 120 minutes post end-of-infusion	± 10 minutes

a: Vital signs to include blood pressure, pulse rate, respiratory rate, oral temperature, and pulse oximetry.

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LIST OF ABBREVIATIONS

ADA Anti-drug antibodies

AE Adverse event

AECA Anti-epithelial cell antibody
ALT Alanine aminotransferase
ANA Antinuclear antibody
AST Aspartate aminotransferase
ATC Anatomical therapeutic chemical

AUC_{0.24} Area under the plasma concentration-time curve from pre-dose (time 0) to 24 hours post-dose

 $AUC_{0\text{--}\infty} \qquad \qquad \text{Area under the plasma concentration-time curve from pre-dose (time 0) to infinity}$

BLQ Below the limit of quantification

BMI Body mass index
BUN Blood urea nitrogen

CAR-T Chimeric antigen receptor and T-cell

CFR Code of Federal Regulations
C3 Complement component 3
CBC Complete blood count

CIC Circulating immune complexes

CIDP Chronic inflammatory demyelinating polyneuropathy

C_{max} Maximum plasma concentration determined directly from the concentration-time profile

CRO Contract research organization

CV Coefficient of variation

CVID Common variable immune deficiency

DEC Dose escalation committee
D5W Dextrose 5% in Water
DIF Direct immunofluorescence
DNA Deoxyribonucleic acid
ECG Electrocardiogram

eCRF Electronic case report form
ESR Erythrocyte sedimentation rate
FcGR2a Fc Gamma R2a receptor
FcRn Neonatal Fc receptor

FDA Food and Drug Administration

GCP Good Clinical Practice

GI Gastrointestinal
HBV Hepatitis B virus
HCV Hepatitis C virus

HIPAA Health Insurance Portability and Accountability Act

HIV Human immunodeficiency virus

IB Investigator's brochure IC Immune complex

ICF Informed consent form

ICH International Conference on Harmonization

IgA Immunoglobulin A
IgG Immunoglobulin G
IgG1-4 Immunoglobulin G1-G4
IgM Immunoglobulin M
IL-12 Interleukin 12

IND Investigational new drug
IRB Institutional review board

ITT Intent-to-treat
IUD Intrauterine devices

IV Intravenous

IVIG Intravenous immunoglobulin

MedDRA Medical Dictionary for Regulatory Activities

NHL Non-Hodgkin lymphoma
PD Pharmacodynamics
PE Physical examination
PK Pharmacokinetic
RBC Red blood cells
RNAseq RNA sequencing

QTcF Corrected QT interval using Fridericia's formula

SAE Serious adverse event SAP Statistical analysis plan SAS Statistical Analysis System

SD Standard deviation

SNP Single nucleotide polymorphism

SOC System Organ Class

SOP Standard operating procedures

SYNT001 A humanized, affinity matured IgG4-kappa monoclonal antibody

t_{1/2} Half-life

TEAE Treatment-emergent adverse event

T_{max} Observed time to reach peak plasma concentration

TNF Tumor necrosis factor ULN Upper limit of normal

UNS Unscheduled

VZV Varicella-zoster virus

WAIHA Warm antibody autoimmune hemolytic anemia

WHO World Health Organization

WHO-DD World Health Organization Drug Dictionary

2 BACKGROUND AND RATIONALE

SYNT001, a humanized, affinity-matured IgG4-kappa monoclonal antibody (mAb), blocks IgG and IgG immune complex (IC) interactions with the neonatal Fc receptor (FcRn) and thereby the major functions of FcRn in protecting IgG and IgG ICs from degradation and their role in downstream signaling events. Specific and high affinity blockade of FcRn with SYNT001 has been shown to increase the catabolism of IgG and IgG IC in healthy volunteers. This predicts that SYNT001 will also accelerate degradation of endogenous circulating IgG autoantibodies and IgG-antigen IC specifically involved in the pathogenesis of autoimmunity. Blocking FcRn interactions with IgG-containing ICs further predicts that SYNT001 will have consequences for innate and adaptive cellular immunity. In the first instance, blocking multimeric IgG IC interactions with FcRn within antigen-presenting cells will result in inhibition of IC-stimulated inflammatory cytokine production and release by these cells. In addition, as FcRn determines the intracellular itinerary of IgG ICs within and among compartments important in cellular immunity, it is anticipated that SYNT001 will block antigen processing and presentation of antigens contained within IC that otherwise lead to CD8⁺ and CD4⁺ T cell activation. Thus, SYNT001 will specifically target immune functions associated with IgG that are involved in certain autoimmune conditions and dismantle their ability to cause disease.

SYNT001 targets key mechanisms contributing to pathology in a variety of IgG-mediated autoimmune disorders, including warm antibody autoimmune hemolytic anemia (WAIHA), pemphigus, and chronic inflammatory demyelinating polyneuropathy (CIDP).

While current treatments for certain autoimmune disorders, including high-dose steroids, immunosuppressants, intravenous immunoglobulin (IVIG), plasmapheresis, and anti-CD20 monoclonal antibodies (mAbs), such as rituximab, can be effective, they are associated with significant adverse effects, as well as delayed or non-durable responses.

Pemphigus is a rare group of blistering autoimmune diseases that affect the skin and mucous membranes. Autoantibodies have been shown to play an important pathogenic role in the mucosal and cutaneous manifestations in patients with pemphigus. Administration of SYNT001, which significantly decreases total IgG, including a corresponding decrease in the level of the pathogenic autoantibodies and the ICs to which they are associated, may lead to a decrease in the mucosal and cutaneous manifestations in patients with pemphigus. Moreover, the ability of SYNT001 to reduce circulating immune complexes (CICs) and the associated innate and adaptive immune responses may allow for further sustained disease modification.

2.1 Study Rationale

This study is being conducted to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity of intravenous (IV) SYNT001 as well as its effects on pemphigus disease activity markers.

2.2 Selection of Doses in this Study

The planned dose levels of SYNT001 for this Phase 1b safety and proof-of-concept study of 10 mg/kg and 30 mg/kg were selected from careful review of the safety, tolerability, and PD effect on total IgG levels after single and repeat dosing of SYNT001 in non-human primates (NHPs), as well as the safety, tolerability, and PD effect on total IgG levels after single ascending doses of SYNT001 in healthy volunteers. In addition, further consideration was given to the desired level of FcRn blockade to achieve suppression of IgG to a range that has been previously correlated with disease remission. Further, we considered the potential effects of inhibiting FcRn function as they relate to immune complex associated innate and adaptive immunity in choosing these dose levels based upon exploratory studies of a single ascending dose of SYNT001 in healthy volunteers. From the NHP studies, single doses of SYNT001 produced a dose-dependent decrease in total IgG and a further decrease was seen with repeated weekly doses up to a maximum 70% reduction at 100 mg/kg. This magnitude of total IgG reduction is approaching the expected maximal effect of 100% inhibition of FcRn function based on murine studies also performed by Syntimmune and others (Nixon et al., 2015; Roopenian et al., 2003). In the recently completed Phase 1a trial with SYNT001 in healthy volunteers a single dose caused a maximum average 50% drop in total IgG with IV dosing at 30 mg/kg. Based on the NHP studies further reductions are expected following multiple dosing. A comparable decrease in pathogenic autoantibodies is also anticipated.

In the NHP studies, relevant adverse effects, mild-to-moderate infusion reactions, were observed only after the third weekly IV administration, concurrent with the development of anti-SYNT001 antibodies. In the recently completed Phase 1a healthy male volunteer study, the doses of SYNT001 up to and including 30 mg/kg have been well tolerated. There were no dose limiting toxicities, serious adverse events, or any other safety concerns identified. No AEs were observed in the 1 and 3 mg/kg dose cohorts. A single Grade 2 AE was observed; a headache in the 10 mg/kg cohort. Other subjects had mild (Grade 1) AEs at 10 mg/kg. In Cohort 4 (30 mg/kg), 5 subjects received SYNT001. All five subjects experienced AEs; all were mild (Grade 1), transient and resolved spontaneously without intervention. Therefore, it is anticipated that the doses selected for this study should be well tolerated and have clinically relevant PD effects in patients with chronic pemphigus (vulgaris or foliaceus). For a summary of findings from the

single dose, clinical study in healthy subjects and further details on the nonclinical findings, please refer to the SYNT001 Investigator's Brochure.

2.3 Compliance Statement

This study will be conducted in compliance with Good Clinical Practice (GCP), including the International Conference on Harmonisation (ICH) Guidelines and FDA regulations, consistent with the principles outlined in the Declaration of Helsinki. In addition, the Investigator agrees to adhere to all applicable local laws and regulatory requirements relevant to the use of new therapeutic agents.

The study will be conducted in compliance with the protocol. The appropriate Institutional Review Boards (IRBs) must approve the protocol, any amendments, and the subject informed consent form (ICF) prior to implementation.

Freely given written informed consent must be obtained from every subject prior to participation in this clinical trial. As part of this procedure, the Investigator must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the study subject is aware of the potential risks, inconveniences, or AEs that may occur. The study subject should be informed that he/she is free to withdraw from the study at any time. He/she will receive all information that is required by federal regulations and ICH guidelines. The Investigator or designee will provide the Sponsor with a copy of the IRB-approved informed consent form prior to the start of the study. The rights, safety, and well-being of participating subjects are the most important considerations and should prevail over interests of science and society.

Study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). This trial will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of 5 once-weekly IV infusions of SYNT001 at different dose levels in subjects with chronic pemphigus (vulgaris or foliaceus).

3.2 Secondary Objectives

The secondary objectives of this study are as follow:

- To determine the PK of SYNT001 following 5 once-weekly 1-hour IV infusions at different dose levels
- To assess the effect of 5 once-weekly doses of SYNT001 at different dose levels on the following PD biomarkers:
 - o Immunoglobulins: IgG, IgG subtypes (IgG1-4), IgA, IgM
 - o Albumin
- To assess the effect of 5 once-weekly doses of SYNT001 at different dose levels on the following disease activity markers:
 - o Serum anti-desmoglein (Dsg) (1 and 3) antibody levels
 - o Pemphigus Disease Area Index (PDAI)
- To assess immunogenicity (anti-SYNT001 antibodies)

3.3 Exploratory Objectives

The exploratory objectives of this study are as follow:

- To assess the effect of 5 once-weekly doses of SYNT001 at different dose levels on the following biomarkers, including:
 - o Serum anti-epithelial cell antibody (AECA) levels by indirect immunofluorescence
 - o Circulating immune complexes (CIC)
 - o Complement component 3 (C3)
 - Exploratory biomarkers (FCGR2A single nucleotide polymorphism-SNP, RNAseq, urine IgG)
 - Immune phenotyping by flow cytometry for CD3⁺CD4⁺ T, CD3⁺CD8⁺ T, monocytes, NK cells and B cells
 - o SYNT001 levels in skin biopsies (optional)
 - o Exploratory biomarkers to investigate immune response associated with pemphigus
- To characterize corticosteroid use during the study

4 STUDY DESIGN

4.1 Study Sites

This study will be conducted at approximately 10 sites in the United States (US).

4.2 Study Endpoints

Primary Outcome Measures: Assessment of safety data (adverse events [AEs], serious adverse events [SAEs], vital sign measurements, ECGs and clinical laboratory tests) will be the primary safety measure.

Secondary Outcome Measures

Pharmacokinetics:

Half-life (t_{1/2}), maximum plasma concentration determined directly from the concentration-time profile (C_{max}), observed time to reach peak plasma concentration (T_{max}), area under the plasma concentration-time curve from pre-dose (time 0) to 24 hours post-dose (AUC₀₋₂₄), and area under the plasma concentration-time curve from pre-dose (time 0) to infinity (AUC_{0-∞})

PD Biomarkers:

- Ig Assessments: Serial assessments of total IgG and IgG subtypes (IgG1-4)
 - o Serial assessments of total IgG and IgG subtypes (IgG1-4)
 - o IgA levels
 - o IgM levels
- Albumin levels

Disease activity markers:

- Serum anti-desmoglein (Dsg) (1 and 3) antibody levels
- Pemphigus Disease Area Index (PDAI) scores

Immunogenicity:

• Anti-SYNT001 antibodies

Exploratory Outcome Measures

Biomarkers, including:

- CIC
- C3
- Serum AECA levels
- Exploratory biomarkers (FCGR2A SNP, RNAseq, urine IgG)

- Immune phenotyping by flow cytometry for measurement of CD3⁺CD4⁺ T, CD3⁺CD8⁺ T, monocytes, NK cells and B cells
- SYNT001 levels in skin biopsies (optional)
- Exploratory biomarkers to investigate immune response associated with pemphigus

Concomitant Treatments

Corticosteroid use

Further details on the statistical and analytical plan for these endpoints are available in Section 12, Statistical Considerations.

4.3 Overview of Study Design

This will be a multicenter, open-label study to assess the safety, tolerability, activity, PK, PD, and immunogenicity of 5 once-weekly IV infusions of SYNT001 to subjects with chronic pemphigus (vulgaris or foliaceus).

Planned doses of SYNT001 to be studied are 10 mg/kg and up to 30 mg/kg. Two cohorts of 8 eligible subjects each will receive 5 once-weekly 60-minute infusions of SYNT001 10 mg/kg or up to 30 mg/kg. Based on review of safety, PD, and clinical outcomes of the first cohort, the dose for the second cohort may be adjusted, but with a maximum dose of 30 mg/kg. Based on review of safety, PD and clinical outcomes from these 2 cohorts, a third cohort of up to 8 subjects may be treated at another dose, with a maximum dose of 45 mg/kg, but may also be lower than 10 mg/kg or between 10 and 30 mg/kg, inclusive.

Cohort	No. of Subjects	Dose
1	8	SYNT001 10 mg/kg
2	8	SYNT001 30 mg/kg

Cohorts will be dosed sequentially beginning with Cohort 1. The first 2 subjects will be dosed at least 24 hours apart. A review of the 24-hour safety data for the first subject will be performed to ensure that there are no overt safety concerns before dosing the second subject. A review of the 7-day safety data for the first 2 subjects will be performed prior to dosing the remaining 6 subjects in the cohort. This evaluation will include a review of AE/SAE reports, vital sign assessments, physical examinations, ECGs and clinical laboratory testing. The seriousness, severity, and relatedness of AEs/SAEs will also be considered in the safety evaluation. Safety data will be reviewed on a continuous basis throughout the study. All data through Day 42

(2 weeks after the last subject's last dose in Cohort 1) will be reviewed before Cohort 2 is initiated. Cohort 2 and Cohort 3, if added, will be dosed per the same schedule.

Safety evaluations will be conducted by a dose escalation committee (DEC). The DEC will consist of the Medical Monitor, an Independent Clinical Expert and a Syntimmune Medical Officer. To assist in the safety assessments, the DEC may request that Investigators, other experts, or members within their organizations review the data and participate in the discussions. Dosing and dose escalation will proceed if the DEC has determined that it would be safe and appropriate to do so. In addition, over the course of the study, the DEC will review any drug-related SAEs to determine if modifications to the study or other measures are necessary to ensure the safety of the subjects.

On days where study drug is administered, vital sign and pulse oximetry measurements will be collected immediately prior to the infusion; 15, 30, and 45 minutes after the start of the infusion; at completion of the infusion; and 30 minutes, 1 hour and 2 hours following completion of the infusion.

On Days 0 and 28, PK blood samples will be collected prior to infusion start and then over the subsequent 48 hours. Subjects will remain at the clinic through the 6-hour PK sample collection and will return to the clinic for the 24- and 48-hour collections. Additional samples will be collected on Days 5 and 33.

On Day 0 photographs will be taken of active lesions. Follow-up photographs will be taken of the same areas on Days 33, 56, 84, and 112. If a subject begins a steroid taper, additional photographs will be taken at the clinic visit during which the decision to begin the taper is made.

Subsequent visits will occur on Days 1, 2, 5, 7, 12, 14, 19, 21, 28, 29, 30, 33, 42 and 56 for safety assessments, study drug dosing, sample collections, and other study procedures.

Subjects also will return to the clinic on Days 84 and 112 for follow-up visits. Subjects whose total IgG is not within 30% of their Day 0 baseline value and not above 500 mg/dL at the Day 112 visit will be referred for further management.

See Table 1 for a schedule of all study events. To assess safety and tolerability, subjects will undergo physical examinations (PEs; including weight), vital sign measurements, clinical (safety) laboratory tests, AE assessments, concomitant medication assessments, and electrocardiograms (ECG).

Note: No vaccinations may be given from within 2 weeks of screening through Day 56. Following Day 56, subjects may receive vaccinations at the discretion of the Investigator.

4.4 Randomization and Blinding

This is an open-label study.

5 STUDY POPULATION

5.1 Target Population

This study will be conducted in approximately 16 male and female subjects (2 cohorts of 8 subjects each) with a confirmed diagnosis of pemphigus (vulgaris or foliaceus); however, a third cohort of up to 8 subjects may be added. Subjects will be enrolled only once in the study and will not be included in subsequent dosing cohorts. Subjects who withdraw for any reason other than an AE and who do not receive study drug or have only received one dose of study drug may be replaced, up to one subject per cohort. Subjects who do not receive all doses of study drug will continue to be followed through all scheduled visits. The maximum number of subjects who may be enrolled in this study is 27 (24 + up to 3 replacements, as necessary). Within each dosing cohort, no more than 3 subjects may be enrolled with pemphigus foliaceus.

5.2 Inclusion Criteria

A subject must meet the following criteria to be eligible for the study:

- 1. Willing and able to read, understand and sign an informed consent form;
- 2. Male or female \geq 18 years of age;
- 3. Documented diagnosis of pemphigus vulgaris or foliaceus based on all 3 of the following criteria:
 - a. Documented clinical history consistent with pemphigus vulgaris or foliaceus (clinical presentation defined as mucosal and/ or skin lesions);
 - b. Presence of Anti-Dsg 1 or 3 antibodies above the upper limit of normal;
 - c. History of at least one positive tissue based test (biopsy, DIF)
- 4. Active disease: Lesions lasting > 2 weeks, and 3 active lesions in skin or mucosa or 2 active lesions with at least one being a skin lesion > 1 cm diameter:
 - a. If treated with rituximab or other anti-CD20 antibodies, last dose > 12 months prior to screening;
 - b. If being treated with other immunosuppressants (i.e., azathioprine, mycophenolate mofetil or cyclosporine), must be on stable dose (< 10% change in dose) for 6 weeks prior to screening;
 - c. If being treated with corticosteroids, must be $\leq 1 \text{mg/kg/day}$ of prednisone or equivalent and stable (< 10% change in dose) for 2 weeks prior to screening;

- d. Allowed topical therapies for pemphigus lesions upon entering the study include petroleum jelly or Aquaphor® for the skin or chlorhexidine for the mouth
- 5. Body mass index (BMI) $18.5 39.9 \text{ kg/m}^2$;
- 6. Has a negative pregnancy test (for women of childbearing potential) documented prior to the first dose of study drug;
- 7. Females of childbearing potential must agree to be abstinent or else use any two of the following medically acceptable forms of contraception (<1% per year failure rate) from the Screening Period through the final study visit: oral contraceptive, condom with or without spermicidal jelly, diaphragm or cervical cap with spermicidal jelly, or intrauterine device (IUD). A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception.
- 8. Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months do not require contraception during the study.
- 9. Males with female partners of childbearing potential, including males who are surgically sterile (post vasectomy), must agree to be abstinent or else use a medically acceptable form of contraception from the screening period through the final study visit.

5.3 Exclusion Criteria

A subject who meets any of the following criteria is ineligible for the study:

- 1. Unable or unwilling to comply with the protocol;
- 2. Active non-hematologic malignancy or history of non-hematologic malignancy in the 3 years prior to screening (exclusive of non-melanoma skin cancer and cervical cancer in situ);
- 3. Positive for HIV or hepatitis C antibody;
- 4. Positive for hepatitis B surface antigen;
- 5. Active infection or history of recurrent infections;
- 6. IVIG treatment within 60 days of screening;
- 7. Received any cytotoxic (other than azathioprine) or mAb therapy in the 3 months prior to screening;

- 8. Any exposure to an investigational drug or device within 30 days prior to screening;
- 9. Plasmapheresis or immunoadsorption within 60 days of screening
- 10. Cellular therapy, including CAR-T, at any time prior to screening
- 11. Use of any immunosuppressive drugs apart from corticosteroids, azathioprine, mycophenolate mofetil, or cyclosporine within 3 months of screening;
- 12. Serum total IgG < 600 mg/dL;
- 13. Subject has any current medical condition that, in the opinion of the Investigator, may compromise their safety or compliance, preclude successful conduct of the study, or interfere with interpretation of the results (e.g., a significant pre-existing illness or other major comorbidity that the Investigator considers may confound the interpretation of the study results);
- 14. Any vaccination within 2 weeks of screening

6 STUDY PROCEDURES

6.1 Informed Consent

All subjects must take part in the informed consent process. Adequate time must be allowed for the subject to ask questions and make a voluntary decision. No protocol-specific procedures, including screening procedures, are to be performed until the subject has signed and dated an IRB-approved ICF. Subjects may withdraw consent at any time. Participation in the study may be terminated at any time without the subject's consent as determined by the Investigator.

6.2 Demographics and Medical History

Demographics (age, gender, race and ethnicity) and medical history will be obtained from the subject and recorded on the source document and eCRF. Medical history will capture the subject's current medical history (current disease processes), past medical status (past disease processes), history of surgery and concomitant treatments, including relevant clinical response to past disease specific treatments and duration as well as dosing of such treatments.

6.3 Physical Examination

A complete physical examination will be performed as outlined in Table 1. The complete PE will include measurements of weight (in kg) and height (in cm; height to be measured only at screening visit) and a review of the following body systems:

- General appearance
- Head, eyes, ears, nose, and throat
- Neck
- Respiratory
- Cardiovascular
- Abdomen
- Neurologic
- Extremities
- Dermatologic
- Lymphatic

Any abnormal and clinically significant findings from the PE must be recorded in the appropriate eCRF. Findings at screening and Day 0 (pre-dose) will be recorded as medical history.

6.4 Pemphigus Disease Area Index (PDAI) Scoring

Pemphigus severity and disease activity will be measured using the PDAI. See Appendix B.

6.5 Vital Sign Measurements

Vital sign measurements will be collected after the subject has been sitting for 5 minutes. Vital sign assessments will include measurements of sitting blood pressure (mm Hg), heart rate (beats per minute), respiration rate (breaths per minute), oral temperature (Celsius). Abnormal results are to be repeated after 5 minutes of rest. Pulse oximetry (%) also is to be measured. See Table 2 for timing window allowances with respect to measurement collection.

On Days 0, 7, 14, 21, and 28, vital sign measurements are to be obtained immediately prior to the infusion; 15, 30, and 45 minutes after the start of the infusion; at completion of the infusion; and 30 minutes, 1 hour and 2 hours following completion of the infusion. Details on the management of mild to moderate and severe infusion reactions can be found in Figure 1 and Figure 2. Abnormalities in vital sign measurements will be graded in severity per the NCI CTCAE scale Version 4.03.

Subjects should be seated quietly for at least 5 minutes in a chair with their backs supported, their feet flat on floor (legs uncrossed), and their arms bared on a hard surface, with the arm slightly abducted and bent, with palm up and the midpoint of upper arm at heart level. Correct cuff and bladder size should be utilized and the same cuff and arm should be used per subject throughout study.

6.6 12-Lead Electrocardiogram (ECG)

Digital 12-lead ECG measurements will be obtained at screening, on Days 0 and 28 at 5 minutes after the completion of the infusion and at the Day 56 visit. Subjects who conduct their Day 12 visit at the investigative site, as opposed to an at-home nurse visit, will have an additional ECG performed. ECGs are to be performed with the subject in a supine position having rested in this position for at least 5 minutes before each reading. ECGs are to be performed in triplicate, each 1 to 2 minutes apart. See Table 2 for timing window allowances with respect to performing ECG.

The following ECG parameters will be collected: PR interval, QRS interval, and QT interval. The ECG findings will be evaluated by a qualified physician for the presence of abnormalities (qualitative assessment). The physician will assess each ECG as normal, abnormal/not clinically significant, or abnormal/clinically significant.

Normal QTcF is ≤ 450 msec.

Abnormalities in the ECG that appear following therapy or that result in clinical signs and symptoms are considered clinically significant for the purposes of this study and will be recorded on the AE eCRF.

6.7 Clinical Laboratory Measurements

Collection time for all safety, PD, and exploratory labs are outlined in Table 1.

Laboratory testing (hematology, urinalysis, serum chemistry, virology, serology, pregnancy tests, PD samples, PK samples, and anti-drug antibody samples) will be performed using established methods by a central laboratory. Safety laboratory panels are defined as listed in Table 3. Blood and urine samples for hematology, serum chemistry, and urinalysis will be prepared using standard procedures. Results will be provided to the Investigator. Aliquots from the PK, biomarker and anti-drug antibody samples may be retained as back-up for additional testing as necessary. Subjects will be in a seated or supine position during blood collection. Full clinical safety lab draws will be collected at Screening and on Days 0, 7, 14, 21, 28, 33, 42, 56, 84 and 112. The total blood draw for each subject who completes the study at Day 112, will be approximately 433 mL. Please refer to the Laboratory Manual for more information.

Table 3: Clinical Laboratory Panels

Hematology	Serum Chemistry	Urinalysis
CBC with differential and blood smear Erythrocyte Sedimentation Rate (ESR)	 Albumin Alkaline phosphatase ALT AST BUN Calcium Carbon dioxide Chloride Creatinine Glucose LDH Phosphorus Potassium Sodium Total and direct bilirubin Total protein Uric acid C-Reactive Protein 	 Appearance Color pH Specific gravity Ketones Protein Glucose Nitrite Urobilinogen Blood/hemoglobin Leukocyte esterase Bilirubin Microscopic examination of sediment: only if the results of the urinalysis dipstick evaluation are positive for blood/hemoglobin

Virology

- Hepatitis C
- Hepatitis B
- HIV
- VZV
- Tetanus

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count; BUN = blood urea nitrogen; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; VZV = varicella-zoster virus

Abnormalities in clinical laboratory tests that are considered clinically significant are to be recorded on the AE electronic case report form (eCRF) page. Laboratory results will be graded using the NCI CTCAE, Version 4.03. If laboratory values constitute part of an event that meets criteria defining it as serious, the event (and associated laboratory values) must be reported as an SAE (see Section 11.3.1).

6.7.1 Pregnancy Testing

Pregnancy testing will be performed for women of childbearing potential at screening and prior to first dose of SYNT001 on Day 0 and Days 56 and 112 (urine or serum test is acceptable however, positive urine tests must be confirmed with serum testing.)

6.7.2 Virology

Testing for HCV antibody, hepatitis B surface antigen, and HIV antibody will be performed at screening.

6.7.3 Serum Tetanus Antibody and Varicella-Zoster Virus Antibody Testing

Samples for serum tetanus antibody and varicella-zoster virus antibody testing are to be collected at baseline (pre-dose, Day 0) and on Day 56 (Follow-Up visit). Testing at Day 56 will not be done for any subject whose baseline titer is below the level of detection. Specifically, if the baseline VZV titer is above the detectable level, but tetanus is not, only the VZV antibody titer will be tested on Day 56. If the Day 56 results are below the baseline value, defined as greater than 30% below the baseline value, or if the subject falls below the level of detection, the subject will be re-tested at Day 84; if still below the baseline value (or level of detection), the subject will be re-tested at Day 112. Any subject whose baseline value for tetanus or VZV was above the detectable level at baseline, and is not within 30% of the baseline value or is below the detectable level by Day 112, will be referred to their primary care physician for further management.

6.7.4 Pharmacokinetics (PK) Sampling

Starting on Days 0 and 28, serum samples will be collected just prior to the start of study drug infusion (pre-dose), at 5 minutes and 2, 4, 6, 24, and 48 hours after the end-of-study drug infusion. Additional samples will be collected on Days 5 and 33. The actual time and date of each blood draw is to be recorded.

Study drug concentration will be used to calculate the following PK parameters: $t_{1/2}$, C_{max} , T_{max} , AUC_{0-24} , and $AUC_{0-\infty}$.

Detailed instructions for sample collection and preparation will be provided in a separate laboratory manual

6.7.5 Pharmacodynamic Sampling

PD samples will be collected for analyses throughout the study. On Days 0, 7, 14, 21, and 28, samples should be collected prior to infusion of study drug. Measurements for albumin PD biomarkers will be derived from the clinical safety laboratory results. Samples for each type of PD will be collected according to the schedule shown in Table 4.

Table 4: Pharmacodynamic/ Activity Assessments

Parameter	Collection Timepoints	
IgG, IgG subtypes (IgG1-4), IgA, IgM	Screening, and Days 0, 1, 2, 5, 7, 12, 14, 19, 21, 28, 29, 30, 33, 42, 56, 84 and 112.	
Circulating immune complexes (CIC)	Days 0, 5, 7, 12, 14, 19, 21, 28, 33, 42, 56, 84 and 112	
• Albumin	Screening, and Days 0, 7, 14, 21, 28, 33, 42, 56, 84 and 112	
Anti-Dsg (1 and 3) antibody titer	Screening, Days 0, 7, 14, 33, 56, 84 and 112	
 Complement component 3 (C3) Anti-epithelial cell antibody (AECA) levels by indirect immunofluorescence 	Days 0, 14, 33, 56, 84 and 112	
Exploratory biomarker (RNAseq, Urine IgG)	Days 0, 14, 33, 56, 84 and 112	
Immune phenotyping by flow cytometry for measurement of CD3 ⁺ CD4 ⁺ T, CD3 ⁺ CD8 ⁺ T, monocytes, NK cells and B cells	Days 0, 28 and 56	
Exploratory biomarker (FCGR2A SNP, via buccal swab)	Day 0	
Exploratory pemphigus immune response biomarkers	Days 0, 5, 7, 12, 14, 19, 21, 28, 33, 42, 56, 84 and 112	

See Table 2 for timing window allowances with respect to measurement collection. Detailed instructions for sample collection (including collection tubes) and preparation will be provided in a separate laboratory manual.

6.7.6 Immunogenicity Testing

Serum samples will be collected for immunogenicity analyses on Days 0 (pre-dose), 14, 28, 56, 84 and 112.

SYNT001 is being developed for the acute and chronic therapy of autoimmune disorders. Although SYNT001 is a humanized IgG4 monoclonal antibody, exposure to SYNT001 in clinical trials could result in the development of anti-drug antibodies (ADAs), with potential consequences ranging from neutralization or lessening of drug efficacy to safety consequences such as allergic reactions. Testing will first detect binding ADAs, then, for all confirmed positive samples, there will be testing for neutralizing effects.

Detailed instructions for sample collection and preparation will be provided in a separate laboratory manual.

6.8 Study Drug Administration

Two cohorts of 8 eligible subjects each will receive 5 once-weekly 60-minute IV infusions of SYNT001 10 mg/kg or up to 30 mg/kg. SYNT001 will be given as a 250-mL IV infusion over 1 hour using a 0.2-micron, inline filter. Based on review of safety data, as well as available and relevant PD results, and clinical outcomes of Cohort 1, a decision about proceeding with Cohort 2 will be made. Based on review of all safety data, available PD results, and clinical outcomes of these 2 cohorts, a third cohort of 8 subjects may be treated at another dose, with a maximum dose of 45 mg/kg, but may also be lower than 10 mg/kg or between 10 and 30 mg/kg, inclusive.

Cohort No.	Study Drug	Dose Level (mg/kg/dose)
1	SYNT001	10 mg/kg
2	SYNT001	30 mg/kg

See Section 9.1 for dosing schedule.

6.9 Prior and Concomitant Medications

All medications a subject receives within 14 days prior to enrollment through the end of the study will be documented on the source document and eCRF. A history of treatments taken for primary disease, even if not taken within the 14 days prior to enrollment, will be collected.

Note: No vaccinations may be given from within 2 weeks of screening through Day 56. Following Day 56, subjects may receive vaccinations at the discretion of the Investigator.

6.10 Adverse Event Assessments

Information regarding the occurrence of AEs will be collected from the time the subject signs the informed consent form and continuing through the last study visit. Findings at screening and Day 0 (pre-dose) will be recorded as medical history. Any known untoward event that occurs beyond the AE reporting period that the Investigator assesses as related to study drug also should be reported as an AE.

Clinical AEs will be graded using the NCI CTCAE, Version 4.03 (Appendix A).

Note: AEs resulting in a subject's permanent discontinuation from the study, regardless of seriousness or relationship to study drug, MUST be promptly reported to the sponsor. Additionally, subjects must be followed until return to normal and/or resolution of the AE.

See Section 11 for more information.

6.11 Photographs

On Day 0 photographs will be taken of active lesions. Follow-up photographs will be taken of the same areas on Days 33, 56, 84 and 112. Subjects who begin a steroid taper will have additional photographs taken at the clinic visit during which the decision to begin the taper is made. A separate manual describing the procedures for taking photographs will be provided.

6.12 Skin Biopsy

Optional skin biopsy samples from lesional or non-lesional skin will be collected on Day 0 predose and on Days 1, 2, 14, 33, 56 and 84 to analyze SYNT001 levels.

7 STUDY ASSESSMENTS

7.1 Screening Period: Day -14 to Day -1

Informed consent must be obtained before any study-specific samples are taken or study-specific tests or evaluations are conducted. The following assessments at the screening visit are to occur within 14 days before dosing. Study eligibility will be based on satisfying all the study inclusion and exclusion criteria.

At the screening visit, information will be collected and subjects will have clinical evaluations as follows:

- Informed consent (Section 6.1)
- Medical history and demographic data (Section 6.2)
- Review inclusion and exclusion criteria (Section 5.2, Section 5.3)
- Complete PE, including height and weight (Section 6.3)
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- 12-Lead ECG (to be obtained in triplicate after 5 minutes of rest in the supine position) (Section 6.6)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section
- Pregnancy test (Section 6.7)
- Hepatitis and HIV screen (Section 6.7)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - Anti-Dsg (1 and 3) antibody titer
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.2 **Enrollment and First Treatment: Day 0**

Study Day 0 is defined as the date the subject is administered their first dose of study drug. On Day 0, subjects will be asked to come to the clinic and the following procedures will be performed prior to the first dose of study drug:

- Complete physical exam (Section 6.3)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature); to be measured immediately prior to the infusion (Section 6.5)
- Pulse oximetry (to be measured immediately prior to the infusion) (Section 6.5)

- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- Pregnancy test (Section 6.7)
- Serum tetanus antibody and VZV antibody (Section 6.7)
- PDAI Score (Section 6.4)
- PK baseline sample collection (collected just prior to the start of the study drug infusion) (Section 6.7)
- Immunogenicity sample collection (collected just prior to the start of study drug infusion) (Section 6.7)
- PD sample collection (collected just prior to the start of the study drug infusion) (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - Anti-Dsg (1 and 3) antibody titer
 - CIC
 - C3
 - AECA
 - FCGR2A SNP, via buccal swab
 - RNAseq
 - Urine IgG
 - Immune phenotyping
 - Exploratory pemphigus immune response biomarkers
- Optional skin biopsy (Section 6.12)
- Photography (Section 6.11)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After the preceding procedures and assessments are completed:

- Study drug administration (record date and time of dose of study drug) (Section 9)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) will be performed at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion (Section 6.5)
- Pulse oximetry will be measured at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion (Section 6.5)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After administration of study drug, the following post treatment procedures and assessments will be performed:

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature): 30 minutes, 1 hour and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Pulse oximetry: 30 minutes, 1 hour and 2 hours following completion of the infusion (Section 6.5)
- PK sample collection at 5 minutes and 2, 4, 6 hours after the end-of-study drug infusion; record collection date and time for each PK sample (Section 6.7)
- 12-Lead ECG (to be obtained in triplicate at 5 minutes after the completion of study drug infusion (Section 6.6)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.3 Follow-up: Day 1

On Day 1 (24 hours \pm 1 hour from end-of-infusion time on Day 0), the subject will return to the clinic and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
- PK sampling (record collection date and time) (Section 6.7)
- Optional skin biopsy (Section 6.12)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.4 Follow-up: Day 2

On Day 2 (48 hours \pm 2 hours from end-of-infusion time on Day 0), the subject will return to the clinic and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
- PK sampling (record collection date and time) (Section 6.7)
- Optional skin biopsy (Section 6.12)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.5 Follow-up: Day 5

On Day 5 (120 hours \pm 4 hours from end-of-infusion time on Day 0), subjects may return to the clinic or be visited by at-home nurse, and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- PK sampling (record collection date and time) (Section 6.7)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Exploratory pemphigus immune response biomarkers
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.6 Treatment Day 7 (Dose 2)

On Day 7 (\pm 6 hours) subjects will return to the clinic and the following procedures are to be performed prior to study drug infusion:

- Complete physical exam (Section 6.3)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature); to be measured immediately prior to the infusion (Section 6.5)
- Pulse oximetry (to be measured immediately prior to the infusion) (Section 6.5)
- PDAI Score (Section 6.4)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- PD sample collection (collected just prior to the start of the study drug infusion) (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titer
 - Exploratory pemphigus immune response biomarkers
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After the preceding procedures and assessments are completed:

- Study drug administration (record date and time of dose of study drug) (Section 9)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral

- temperature) will be performed at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion (Section 6.5)
- Pulse oximetry will be measured at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion (Section 6.5)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After administration of study drug, the following post treatment procedures and assessments will be performed:

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature): 30 minutes, 1 hour and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Pulse oximetry: 30 minutes, 1 hour and 2 hours following completion of the infusion (Section 6.5)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.7 Dose 2 Follow-up Day 12

On Day 12 (\pm 6 hours) the subject may return to the clinic, or be visited by at-home nurse, and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Exploratory pemphigus immune response biomarkers
- If visit performed at the study site: 12-Lead ECG to be obtained in triplicate (Section 6.6)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.8 Treatment Day 14 (Dose 3)

On Day 14 (\pm 6 hours) subjects will return to the clinic and the following procedures are to be performed prior to study drug infusion:

- Complete physical exam (Section 6.3)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature); to be measured immediately prior to the infusion (Section 6.5)

- Pulse oximetry (to be measured immediately prior to the infusion) (Section 6.5)
- PDAI Score (Section 6.4)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- Immunogenicity sample collection (collected just prior to the start of study drug infusion) (Section 6.7)
- PD sample collection (collected just prior to the start of the study drug infusion) (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - Anti-Dsg (1 and 3) antibody titer
 - CIC
 - C3
 - AECA
 - RNAseq
 - Urine IgG
 - Exploratory pemphigus immune response biomarkers
- Optional skin biopsy (Section 6.12)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After the preceding procedures and assessments are completed:

- Study drug administration (record date and time of dose of study drug) (Section 9)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) will be performed at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion (Section 6.5)
- Pulse oximetry will be measured at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion (Section 6.5)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After administration of study drug, the following post treatment procedures and assessments will be performed:

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature): 30 minutes, 1 hour and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Pulse oximetry: 30 minutes, 1 hour and 2 hours following completion of the infusion (Section 6.5)
- Concomitant medication assessment (Section 6.9)

• AE assessment (Section 6.10)

7.9 Dose 3 Follow-up Day 19

On Day 19 (\pm 6 hours) the subject may return to the clinic, or be visited by an at-home nurse, and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Exploratory pemphigus immune response biomarkers
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.10 Treatment Day 21 (Dose 4)

On Day 21, (\pm 6 hours) subjects will return to the clinic and the following procedures are to be performed prior to study drug infusion:

- Complete physical exam (Section 6.3)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature); to be measured immediately prior to the infusion (Section 6.5)
- Pulse oximetry (to be measured immediately prior to the infusion) (Section 6.5)
- PDAI Score (Section 6.4)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- PD sample collection (collected just prior to the start of the study drug infusion) (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Exploratory pemphigus immune response biomarkers
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After the preceding procedures and assessments are completed:

- Study drug administration (record date and time of dose of study drug) (Section 9)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) will be performed at 15, 30, and 45 minutes after the start of the infusion

and at completion of the infusion (Section 6.5)

- Pulse oximetry will be measured at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion (Section 6.5)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After administration of study drug, the following post treatment procedures and assessments will be performed:

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature): 30 minutes, 1 hour and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Pulse oximetry: 30 minutes, 1 hour and 2 hours following completion of the infusion (Section 6.5)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.11 Treatment Day 28 (Dose 5)

On Day 28 (\pm 6 hours), subjects will return to the clinic and the following procedures are to be performed prior to study drug infusion:

- Complete physical exam (Section 6.3)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature); to be measured immediately prior to the infusion (Section 6.5)
- Pulse oximetry (to be measured immediately prior to the infusion) (Section 6.5)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- PDAI Score (Section 6.4)
- PK sampling (collected just prior to the start of the study drug infusion; record collection date and time for each PK sample) (Section 6.7)
- Immunogenicity sample collection (collected just prior to the start of study drug infusion) (Section 6.7)
- PD sample collection (collected just prior to the start of the study drug infusion) (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Immune phenotyping
 - Exploratory pemphigus immune response biomarkers
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After the preceding procedures and assessments are completed:

- Study drug administration (record date and time of dose of study drug) (Section 9)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) will be performed at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion (Section 6.5)
- Pulse oximetry will be measured at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion (Section 6.5)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

After administration of study drug, the following post treatment procedures and assessments will be performed:

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature): 30 minutes, 1 hour and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Pulse oximetry: 30 minutes, 1 hour and 2 hours following completion of the infusion (Section 6.5)
- PK sample collection at 5 minutes and 2, 4, 6 hours after the end-of-study drug infusion; record collection date and time for each PK sample (Section 6.7)
- 12-Lead ECG (to be obtained in triplicate at 5 minutes after the completion of study drug infusion (Section 6.6)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.12 Follow-up Day 29

On Day 29 (24 hours \pm 1 hour from end-of-infusion time on Day 28), the subject will return to the clinic and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
- PK sampling (record collection date and time) (Section 6.7)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.13 Follow-up Day 30

On Day 30 (48 hours \pm 2 hours from end-of-infusion time on Day 28), the subject will return to the clinic and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
- PK sampling (record collection date and time) (Section 6.7)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.14 Follow-up Day 33

On Day 33 (120 hours \pm 4 hours from end-of-infusion time on Day 28), subjects will return to the clinic and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- PDAI Score (Section 6.4)
- PK sampling (record collection date and time) (Section 6.7)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titer
 - C3
 - AECA
 - RNAseq
 - Urine IgG
 - Exploratory pemphigus immune response biomarkers
- Optional skin biopsy (Section 6.12)
- Photography (Section 6.11)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.15 Follow-up Day 42

On Day 42 (\pm 3 days), subjects will return to the clinic and the following procedures are to be performed:

- Complete physical exam (Section 6.3)
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- PDAI Score (Section 6.4)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Exploratory pemphigus immune response biomarkers
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.16 Follow-up Day 56

On Day 56 (\pm 5 days), subjects are to return to the clinic and the following procedures are to be performed:

- Complete physical exam (Section 6.3)
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- Pregnancy test (Section 6.7)
- 12-Lead ECG (to be obtained in triplicate after 5 minutes of rest in the sitting position) (Section 6.6)
- Serum tetanus antibody and VZV antibody; Testing at Day 56 will not be done for any subject whose baseline titer is below the level of detection. See Section 6.7.3 for additional information.
- Immunogenicity sample collection (Section 6.7)
- PDAI Score (Section 6.4)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC

- Anti-Dsg (1 and 3) antibody titer
- C3
- AECA
- RNAseq
- Urine IgG
- Immune phenotyping
- Exploratory pemphigus immune response biomarkers
- Optional skin biopsy (Section 6.12)
- Photography (Section 6.11)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.17 Follow-up Day 84

On Day 84 (\pm 5 days), subjects are to return to the clinic and the following procedures are to be performed:

- Complete physical exam (Section 6.3)
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- Serum tetanus antibody and VZV antibody testing if required. See Section 6.7.3 for additional information.
- Immunogenicity sample collection (Section 6.7)
- PDAI Score (Section 6.4)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titer
 - C3
 - AECA
 - RNAseq
 - Urine IgG
 - Exploratory pemphigus immune response biomarkers
- Optional skin biopsy (Section 6.12)
- Photography (Section 6.11)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.18 Follow-up Day 112 (End-of-Study) or Early Termination Visit

On Day 112 (\pm 5 days), subjects are to return to the clinic and the following procedures are to be performed:

- Complete physical exam (Section 6.3)
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- Pregnancy test (Section 6.7)
- Serum tetanus antibody and VZV antibody testing if required. See Section 6.7.3 for additional information.
- Immunogenicity sample collection (Section 6.7)
- PDAI Score (Section 6.4)
- PD sample collection (Section 6.7)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titer
 - C3
 - AECA
 - RNAseq
 - Urine IgG
 - Exploratory pemphigus immune response biomarkers
- Photography (Section 6.11)
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

8 REMOVING SUBJECTS FROM STUDY

Every reasonable effort will be made to keep the subject in the study; however, if a subject is withdrawn from the study, every effort will be made by the Investigator to complete and report the reasons for withdrawal as thoroughly as possible. The reason(s) for termination must be clearly documented on the appropriate page of the eCRF. Once a subject discontinues from the study for any reason, every effort will be made to collect all clinical and laboratory data as scheduled for the Early Termination Visit (See Table 1). A termination eCRF must be completed for all enrolled subjects.

8.1 Subject Withdrawal

A subject's participation in the study may be prematurely discontinued for any of the following reasons:

- 1. The subject wishes to withdraw from the study.
- 2. Request by a regulatory agency (e.g., Institutional Review Board).
- 3. Subject experiences a significant or intolerable AE.
- 4. The subject experiences a significant adverse change in vital signs, PE findings, or a clinical laboratory parameter.
- 5. The subject has a need for a concomitant medication that is not permitted by the study protocol.
- 6. The subject experiences generalized impairment or mental incompetence that would result in the subject being unable to understand his or her participation in the study.
- 7. If, in the Investigator's medical judgment, further participation would be injurious to the health and well-being of the subject, or is not in the best interest of the subject.
- 8. Administrative reasons, such as subject non-compliance or a major protocol violation.

Subjects who are withdrawn from this study due to an AE determined to be related to study drug are to be followed until there is either:

- Resolution or stabilization of the AE determined to be related
- The subject is lost to follow-up
- The event is otherwise explained

If there is a persistent AE contributing to discontinuation that is determined to be related to SYNT001, subjects must be followed with appropriate medical management until resolution or stabilization.

A reasonable effort should be made to contact any subject lost to follow-up during the study to complete assessments and retrieve any outstanding data. If the subjects are unreachable by telephone after three (3) attempts, the minimum of a registered letter should be sent requesting that contact be made with the Investigator to report survival information.

8.2 Study Discontinuation

Syntimmune Inc. has the right to terminate or to stop the study at any time. Reasons for study discontinuation may include, but are not limited to the following:

- The incidence or severity of AEs in this or other related studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory
- Drug supply issues
- Excessive subject self-withdrawal
- Significant protocol violations (e.g., violation of eligibility criteria, dosing errors, missing data for study endpoint analysis)

8.3 Replacements

Enrolled subjects withdrawn for a reason other than an AE will be replaced if they have not been dosed or have only received one dose of study drug at the time of discontinuation, up to one subject per cohort. Subjects who do not receive all doses of study drug will continue to be followed through all scheduled study visits.

8.4 Stopping Rule

8.4.1 Dose-Escalation Stopping Rule

Dose escalation decisions will be made by a Dose Escalation Committee (DEC) and will be based on safety and pharmacodynamic evaluations including but not limited to, dose-limiting toxicities, AEs, SAEs, and total IgG levels.

Dose-limiting toxicity (DLT) will be defined generally as severe (Grade 3) AEs occurring in \geq 2 subjects that are determined to be clinically significant and considered related to study drug.

If 2 or more subjects at any time in any cohort (8 total subjects per cohort) have Grade 3 AEs that are determined to be clinically significant and considered to be related to study drug, dosing will be halted within that cohort and dose-escalation to a higher dose will not occur. If the dose-escalation stopping rule is met during Cohort 1 (10 mg/kg) all safety data and all available pharmacodynamics will be reviewed and the cohort may resume (if applicable) or a new cohort may be added at a dose at least 50% lower than the 10 mg/kg dose. If the stopping rule is not met in Cohort 1, dose-escalation may proceed up to a maximum of 30 mg/kg. If the dose-escalation stopping rule is met for the first time during Cohort 2, all safety data and all available pharmacodynamics will be reviewed and the cohort may resume (if applicable) or a new cohort may be added at a dose a minimum of 30% lower than the Cohort 2 dose. If the stopping rule is not met in Cohort 2, dose-escalation may proceed up to a maximum of 45 mg/kg; however, this cohort may also receive a dose equal to or less than 30 mg/kg based on evaluation of all safety and pharmacodynamic data.

8.4.2 Study Stopping Rule

If any subject experiences a life-threatening AE (Grade 4) that is considered to be related to study drug, further dosing in all enrolled subjects will be suspended until the DEC has evaluated the event and determined the appropriate course of action. At any time during the study, the study may be discontinued if the DEC determines that further drug exposure would pose an undue risk to subjects.

8.4.3 Individual Stopping Rule

Dosing for any individual subject will be discontinued (i.e., no further study drug will be given to that subject) if the subject experiences any study drug-related SAE or any study drug-related non-SAE adverse event that, in the judgement of the Investigator (following consultation with the Medical Monitor, if desired) suggest that it could be unsafe to administer further study drug to that subject. Additionally, a subject will be discontinued from further treatment with study drug, at the discretion of the Investigator with consultation with the Medical Monitor, if they require a significant increase in dose(s) of anti-pemphigus medication(s) for the management of pemphigus.

9 STUDY DRUG

For detailed information regarding SYNT001 preparation and administration, refer to the Pharmacy Manual.

9.1 SYNT001

SYNT001 is provided in vials containing 5 mL SYNT001 (extractable volume) at a nominal concentration of 50 mg/mL. The product is supplied as a liquid at pH 6.5 ± 0.5 . SYNT001 is diluted in Dextrose 5% in Water (D5W) to prepare the solution for infusion. SYNT001 will be infused via IV in 250 mL over 1 hour using a 0.2-micron, inline filter.

Two cohorts of 8 eligible subjects each will receive 5 once-weekly 60-minute infusions of SYNT001 in planned doses of 10 mg/kg or 30 mg/kg. Based on review of safety, PD, and clinical outcomes of these two cohorts, a third cohort of up to 8 subjects may be treated at another dose, with a maximum dose of 45 mg/kg, but may also be lower than 10 mg/kg or between 10 and 30 mg/kg, inclusive.

The specification for host cell DNA in SYNT001 is < 2 pg/mg, the limit of quantitation of the assay. To comply with regulatory guidelines, which specify a maximum level of 10 ng host cell DNA per dose, dosing is limited to 5000 mg of SYNT001. Therefore, the maximum subject weight allowed for enrollment into the 30 mg/kg dose cohort is 166 kg and the maximum subject weight allowed for enrollment into the highest dose possible in this study (45 mg/kg)is 111 kg.

9.2 Cohort Dosing

Cohorts will be dosed sequentially beginning with Cohort 1. The first 2 subjects will be dosed at least 24 hours apart. A review of the 24-hour safety data for the first subject will be performed to ensure that there are no overt safety concerns before dosing the second subject. A review of the 7-day safety data for the first 2 subjects will be performed prior to dosing the remaining 6 subjects in the cohort. Cohort 2, and Cohort 3 if added, will be dosed per the same schedule

9.3 Timing of Dosing

On Days 0, 7, 14, 21, and 28, subjects will receive a 60-minute IV infusion of SYNT001 in the morning. The date and time the dose is administered will be recorded.

9.4 Identity of Investigational Products

All supplies of SYNT001 will be supplied by Syntimmune and must be stored refrigerated (2°C to 8°C/36°F to 46°F) in the carton and protected from light, in a securely locked area, accessible

to authorized persons only, until needed for dose preparation. Qualified site personnel will inventory the investigational product received and will maintain records of disposition of the drug, including dates, quantity and use.

9.5 Investigational Product Retention at Study Site

The Investigator (or designee) is responsible for maintaining accurate accountability records of the investigational product throughout the clinical study. All study drug received at the site must be inventoried and accounted for in an accountability log provided by the Sponsor. All dispensing and accountability records will be available for Sponsor review. Study drug accountability will be verified during on-site monitoring visits.

Upon the completion or termination of the study, and upon written authorization from the Sponsor, or its representative, all unused and/or partially used study drug should be returned or destroyed at the investigational site, as specified by Sponsor. It is the Investigator's responsibility to ensure that the Sponsor, or its representative, has provided written authorization that procedures for proper disposal of the study drug have been established, and that appropriate records of the disposal are documented and maintained. No unused study drug may be disposed until fully accounted for by the Sponsor monitor (or designee)

9.6 Warnings and Precautions

Note: Subjects must not receive any vaccinations from within 2 weeks of screening until Day 56.

9.6.1 Infusion Reaction

SYNT001 will be given as an IV infusion over 1 hour. As with all mAbs administered by IV infusion, infusion reactions are possible. In nonclinical testing of SYNT001 in NHPs, clinical observations were limited to infusion reactions due to the immunogenicity of SYNT001 in NHPs. These reactions included transient emesis/vomitus which typically occurred within 1 hour of dosing at all dose groups, but only after the third weekly infusion following the development of ADAs. Transient histamine-type responses were noted 30 minutes post-dose in some animals in all dose groups, but only following the third weekly infusion as above. These reactions were consistent with a histamine reaction (decreased activity, periocular swelling, erythema, facial flushing, eyelids partially/completely closed, and/or generalized weakness). With the exception of vomitus/emesis and red skin discoloration associated with injection or blood draw sites, these observations spontaneously resolved within 1-hour post-dose. Subsequent pretreatment with intramuscular diphenhydramine prevented further histamine-type reactions. All doses of SYNT001 were administered by bolus infusion over approximately 5 minutes in the NHP

studies. However, all of the observed infusion reactions (including vomitus/emesis and histamine-type reactions) associated with ADAs are not at all predictive of what may occur in humans (Bugelski and Treacy, 2004; Ponce et al., 2009) and furthermore, are not considered relevant to predicting responses in humans [ICH S6(R1) 2011].

Typically, infusion reactions to monoclonal antibodies observed in human studies develop within 30 minutes to 2 hours after the initiation of drug infusion, although symptoms may be delayed for up to 24 hours. Most are mild in severity, although severe and even fatal reactions can occur.

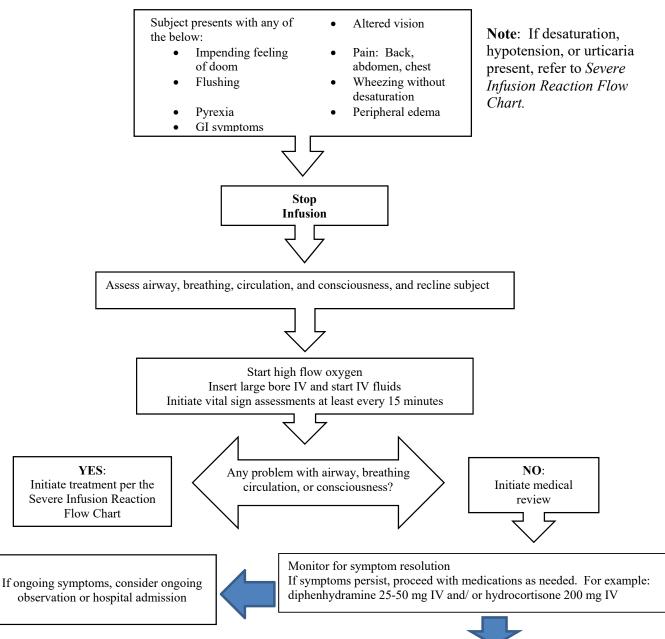
Guidelines for Grading and Management of Allergic or Infusion-Related Reactions

Allergic and/or infusion-related reactions include hypersensitivity reactions and cytokine release syndromes. These reactions are experienced by patients during or within hours of the infusion of monoclonal antibody therapy. Symptoms can include flushing, alterations in heart rate and blood pressure, dyspnea, bronchospasm, back pain, fever, urticaria, edema, nausea, and all types of rashes. Anaphylaxis is recognized as a severe, life-threatening, generalized, or systemic reaction. This is a medical emergency characterized by rapidly developing life-threatening airway and/or breathing and/or circulation problems usually associated with skin or mucosal changes.

Management of Grade 1 infusion reactions include interrupting the infusion or decreasing the rate of infusion by 50% and observing. Symptoms may also be treated as needed with medications such as diphenhydramine, hydrocortisone or acetaminophen, either alone or in combination, depending on the subject's signs and symptoms. If the infusion is interrupted or the infusion rate is decreased, it is important to note that all study drug infusions must be completed within 4 hours of SYNT001 administration.

Management of Grade 2 and higher infusion reactions should include stopping the infusion of study drug. See Figure 1 and Figure 2 for details on the management of Grade 2 and Grade 3 or higher infusion reactions. The severity of and management of allergic or infusion-related reactions will be graded and managed using NCI CTCAE Version 4.03 (see Table 5).

Figure 1: Management of Moderate (Grade 2) Infusion Reactions



If symptoms and signs resolve completely either spontaneously or after administration of diphenhydramine with or without hydrocortisone, consider rechallenge:

Wait at least 20 minutes following medication administration before commencing rechallenge at an infusion rate of 50% or less of the initial infusion rate or

Consider pre-medicating the subject with the same medication(s) 20-30 minutes in advance of subsequent administrations of SYNT001 and starting infusion at 50% of the planned infusion rate for the first 30 minutes, then returning to the intended infusion rate in the absence of any infusion reaction. If the infusion is interrupted or the infusion rate is decreased, it is important to note that all study drug infusions must be completed within 4 hours of SYNT001 administration.

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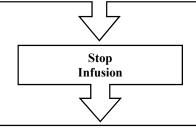
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Figure 2: Management of Severe (Grade 3 or higher) Infusion Reactions

Subject presents with any of the below:

- Urticaria
- Airway threatened by angioedema
- Angioedema: Lip, mouth, facial swelling
- Respiratory compromise wheezing, dyspnea, stridor or hypoxia (O2 saturation < 90%)
- BP < 90 mmHg SBP or >30% decrease from patient baseline



Start basic life support:

- High oxygen flow
- On bed, head down, legs up
- Large bore IV cannula, 1 L normal saline STAT
- Initiate vital signs at least every 15 minutes



Consider (under medial direction):

Epinephrine 1:1000

• 0.3 mg (0.3 mL) IM into lateral thigh



Airway Threatened: Nebulized epinephrine 1:1000, 3–5 mL (3–5 mg)

Bronchospasm: Nebulized salbutamol 5 mg

(Wheeze or Hypoxia) Consider: Intubation / nebulized epinephrine

Hypotension: Place on cardiac monitor

(Systolic BP <100 mmHg) Further epinephrine 1:1000, 0.3 mg IM and

IV normal saline bolus 20 mL/kg STAT as needed

Have vasopressin on hand



Transfer to Emergency Room/ICU Observe until all symptoms resolved.

Table 5: Grading and Management of Allergic or Infusion-Related Reactions

Adverse Event	Grade				
	1	2	3	4	5
Infusion- Related Reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids): prophylactic medications indicated for ≤ 24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement, hospitalization indicated for clinical sequelae	Life- threatening consequences; urgent intervention required	Death
Allergic Reaction	Transient flushing or rash, drug fever < 38.0°C. Intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids): prophylactic medications indicated for ≤ 24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement, hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life- threatening consequences; urgent intervention required	Death
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticarial; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life- threatening consequences; urgent intervention required	Death
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids): prophylactic medications indicated for ≤ 24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement, hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life- threatening consequences; pressor or ventilator support indicated	Death

Abstracted from NCI CTCAE Version 4.03.

9.6.2 Potential Immune Effects

An antibody blocking FcRn is anticipated to have several effects. These include acceleration of catabolism of IgG, but not other immunoglobulin isotypes such as IgA and IgM, leading to dose-dependent decreases in circulating IgG levels by up to an estimated 50% from the baseline levels after a single dose and further decreases after multiple doses up to a 70% to 80% reduction. Based on studies in humans, it is expected that with a single dose, the nadir of this effect will occur approximately 5 days after dosing. The time course of recovery of IgG following dosing in the Phase 1a study suggests that a return to within 30% of baseline levels observed at pretreatment occurs within 4 weeks after a single dose and within 4 weeks after multiple doses as shown in NHPs.

Given the normal adult range of IgG of 500 to 1600 mg/dL (Agarwal and Cunningham-Rundles, 2007; Furst, 2009; Gonzalez-Quintela et al., 2008; Jolliff et al., 1982; Keystone et al., 2007; McMillan et al., 1997; van Vollenhoven et al., 2013), with a mean of 1150 mg/dL, a 50% decrease in the mean would be to 575 mg/dL and a 50% decrease from the low end of the normal range used for the inclusion criteria of 600 mg/dL would be to 300 mg/dL. An 80% decrease from baseline after multiple doses would result in IgG levels of 230 mg/dL and 120 mg/dL, respectively. While these levels are in the range found in patients with primary humoral immunodeficiency (Ameratunga et al., 2013), the levels will be transient. Further, as reported for other therapies used for pemphigus, the temporary (ie, less than 4 months) depletion of IgG (up to 95% reduction of total IgG as seen with immunoadsorption) does not appear to impart an increased risk of infection (Eming and Hertl, 2006; Furst, 2009; Keystone et al., 2007; Schmaldienst et al., 2001; van Vollenhoven et al., 2013). Study subjects will be monitored clinically for any infection. Further, commercial IVIG can be given to reverse the low IgG levels in case of a bacterial infection occurring while their IgG levels are decreased.

An antibody blocking FcRn is expected to also down modulate innate and adaptive immunity and the catabolism of IgG-containing immune complexes (IC). Specifically, it is expected that anti-FcRn will promote the clearance of IgG-containing ICs and the effects of these IC on stimulating innate immune cell production of inflammatory cytokines (e.g., IL-12, interferon-γ, and tumor necrosis factor [TNF]) and inhibit the processing and presentation of antigens contained within IC and thus the antigen-specific activation of CD4⁺ and CD8⁺ T-cells. Therefore, subjects with pre-existing conditions that are dependent upon IgG antibodies, such as chronic infections (e.g., HIV, HBV or HCV), will be excluded from this study, as will subjects with active infection in general.

SYNT001 administration could decrease the level of protective antibodies from prior vaccinations. Protective antibody levels for tetanus and varicella-zoster virus (chickenpox) are to be tested in accordance with Section 6.7.3.

10 CONCOMITANT MEDICATION AND TREATMENT

All treatments a subject receives within 14 days prior to enrollment through the end of the study will be documented. Concomitant medication and treatment for co-existing conditions, including those for pemphigus, are permitted if not excluded below. Topical antibiotics are permitted to treat active infections that occur on study. Topical or systemic treatments for oral candidiasis are permitted. Topical lidocaine for transient pain relief is acceptable as needed. Significant increases in anti-pemphigus medications will result in subjects being discontinued from the study. Concomitant treatment that is medically indicated for any AEs the subject experiences during the study are permitted. Premedication is discouraged as prophylaxis against AEs or infusion reactions unless medically indicated from either past medical history, prior infusion reactions or AEs resulting from SYNT001 infusions.

Use of the following treatments will not be permitted during the study unless otherwise specified:

- Rituximab or other anti-CD20 antibody
- Monoclonal antibodies other than study drug
- Any immunosuppressive drugs apart from corticosteroids, azathioprine, mycophenolate mofetil, or cyclosporine.
- Topical steroids
- Any dietary herbal supplements
- Any investigational drug or device
- Any vaccinations through Day 56. Following Day 56, subjects may be vaccinated at the discretion of the Investigator.

If over a period of at least two weeks on study drug, a subject on corticosteroids shows the absence of new lesions and significant healing of lesions that existed at study baseline, a slow corticosteroid taper may be started as per the following suggested schedule

- If on > 30 mg of prednisone per day, decrease by 10 mg every two weeks until a dose of 30 mg per day then decrease by 5 mg every two weeks
- If on < 30 mg of prednisone per day, decrease by 5 mg every two weeks

In cases in which concomitant medications are used, details to be recorded include the following: medication name, start date and time, stop date and time, dose, route, frequency, and reason for use. The concomitant medication names are to be coded using the World Health Organization (WHO) Drug Dictionary (WHO-DD March 2013, Type B2 or later) and classified by anatomical therapeutic chemical (ATC) categories.

11 SAFETY

11.1 Safety Parameters

Clinical and laboratory AEs will be graded using the NCI CTCAE; Version 4.03 (See Appendix A).

Subjects will be monitored throughout the treatment and follow-up period for occurrence of AEs (acute, delayed, and/or cumulative), as well as for changes in clinical status, vital sign measurements, and laboratory data (including PD). Safety parameters to be measured/assessed include PEs, vital sign measurements, hematology, serum chemistries, urinalysis, and ECG.

11.2 Adverse Event Definition

An AE is defined as any untoward medical occurrence in a clinical trial subject associated with the use of a drug, whether considered drug related. An AE can be an unfavorable and unintended sign (e.g., an abnormal laboratory value finding), a symptom, or a disease temporally associated with the use of a drug, without judgment as to causality. An AE can arise from use of the drug (e.g., use in combination with another drug) and from any route of administration, formulation or dose, including an overdose. An AE also includes, but is not limited to, any clinically significant worsening of a pre-existing condition. Examples include:

- Any sign, symptom, physical finding, or laboratory result that has worsened in nature, severity or frequency compared to baseline;
- Reactions from an investigational drug, including those occurring because of an overdose, abuse of the study drug, withdrawal phenomena, sensitivity or toxicity;
- Concurrent illness that was not present or worsens in nature, severity, or frequency compared to baseline;
- Injury or accident; and/or
- Exacerbation of a pre-existing condition.

For data collection, all untoward events that occur after informed consent through the last study visit are to be recorded on eCRFs by the investigational site.

While pregnancy alone is not considered as an AE or SAE, any pregnancy complication(s) should be recorded as an AE(s) or SAE(s) (if applicable). Elective abortions without complications should not be regarded as AEs, unless they were therapeutic abortions (see below). Hospitalization for normal delivery of a healthy newborn should not be considered an SAE. If a female subject becomes pregnant during the conduct of the study, the Investigator must notify the Sponsor according to the procedures provided in Section 11.3.8).

11.3 Evaluating Adverse Events

The Investigator will determine the seriousness, intensity, and causality of an AE associated with the use of the study drug (i.e., events where there is a reasonable possibility that the event may have been caused by the study drug) based on the definitions that follow.

11.3.1 Serious Adverse Events

(Notify Medpace Safety within 24 hours; document on eCRF)

The SAE definition and reporting requirements are in accordance with Title 21 Part Code of Federal Regulations (CFR) 312.32 and the Guidance for Industry and Investigators Safety Reporting Requirements for Investigational New Drug (INDs) and Bioavailability /Bioequivalence Studies.

SAE: An AE is considered "serious" if, in the view of either the Investigator or sponsor, it results in any of the following outcomes:

• <u>Death:</u> This includes any death that occurs while the subject is "on study" through the last study visit.

Note: Death is an outcome of an AE, and not an AE. The event(s) that caused death (e.g., illness, accident) is the SAE. Death due to any other cause(s) must also be reported as an outcome of the reportable SAE.

- <u>Life-threatening adverse drug event:</u> An AE or suspected adverse reaction is considered "life threatening" if, in the view of either the Investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization:

In the absence of an AE, the Investigator should not report hospitalization or prolongation of hospitalization. This is the case in the following situations:

- Hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol
- Hospitalization or prolongation of hospitalization is part of routine procedure followed by study center

- Hospitalization for survey visits or annual physicals
- Hospitalization for observation with release within 24 hours

In addition, a hospitalization planned before the start of the study for a pre-existing condition, which has not worsened, does not count as an SAE.

- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect
- <u>Important medical event:</u> An event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

11.3.2 Overdose

An overdose is defined as a significant variation from the recommended/scheduled dosage for a product. The dosing for this study will be conducted in a controlled clinical setting and an overdose is not anticipated. However, in the event of an accident, for this study, an overdose of SYNT001 is considered a dose that is two-fold higher than the intended dose for the subject.

11.3.3 Non-Serious Adverse Events

(Document on eCRF)

All other AEs, not fulfilling the previous definitions, are classified as non-serious.

11.3.4 Protocol-Related Adverse Events

AEs that are not test drug related may nevertheless be considered by the Investigator or the Medical Monitor to be related to the conduct of the clinical study. That is, the event may be related to the fact that a subject is participating in the study. For example, a protocol-related AE may be an event that occurs during a screening period or that is related to a procedure required by the protocol.

11.3.5 Assessment of Causality

A medically qualified Investigator must assess the relationship of any AE (including SAEs) to the use of the investigational product, as related or not related, based on clinical judgment and using all available information, and may include consideration of the following factors:

- Possible alternative causes of the AE, including the disease under treatment, pre-existing conditions, concomitant use of other drugs, and presence of environmental or genetic
- The temporal association between drug exposure and onset of the AE.
- Whether the manifestations of the AE are consistent with known actions or toxicity of the investigational product.
- The AE resolved or improved with decreasing the dose or stopping use of the investigational product (dechallenge). Judgment should be used if multiple products are discontinued at the same time.

The causal relationship between the study medication and the AE will be assessed using one of the following categories:

Not Related: Factors consistent with an assessment of Not Related include:

- Temporal relationship is lacking (e.g., the event did not occur within a reasonable time frame following administration of the study medication); or
- Other causative factors more likely explain the event (e.g., a pre-existing condition, other concomitant treatments).

Related: Factors consistent with an assessment of Related include:

- There is a positive temporal relationship (e.g., the event occurred within a reasonable time frame following administration of study medication); or
- The AE is more likely explained by the investigational product than by another cause (i.e., the AE shows a pattern consistent with previous knowledge of the investigational product or the class of the investigational product)

11.3.6 **Recording Adverse Events**

All AEs (including SAEs) are to be accurately recorded on the Adverse Event page of the subject's eCRF. The severity of each AE will be graded using the NCI CTCAE, Version 4.03. The date of onset as well as the end date of the event also should be recorded or the event should be entered as "ongoing". In addition, the method used to treat the AE and the outcome of the AE also will be noted. The Investigator will assess the relationship of the event to study drug.

11.3.7 **Planned Hospitalization**

A hospitalization planned by the subject prior to the first dose of study medication is considered a therapeutic intervention and not the result of a new SAE and should be recorded as medical

history. If the planned hospitalization or procedure is executed as planned, the record in the subject's medical history is considered complete. However, if the event/condition worsens during the trial, it must be reported as an AE.

11.3.8 Reporting Pregnancies

If a female subject or the female partner of a male subject becomes pregnant during the course of the study, the Investigator must report the pregnancy to the Medpace Safety using the **Pregnancy Reporting Form** within **24 hours** of becoming aware of the event. The Investigator must obtain consent to collect pregnancy information (including the status of the newborn, if applicable).

If some of the information required for completion of the Pregnancy Reporting Form is unavailable at the time of the initial report, follow-up reports will be completed and submitted within 24 hours of becoming aware of the new information. Any pregnancy will be followed through delivery for the observation of any SAEs. Any SAE that occurs during pregnancy must be recorded on the SAE report form in the EDC system (e.g., maternal serious complications, therapeutic or spontaneous abortion, ectopic pregnancy, stillbirth, neonatal death, congenital abnormality, birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs (See Section 11.3.9).

11.3.9 Serious Adverse Event Reporting

11.3.9.1 Governing Regulatory Requirements

Compliance with this request for prompt reporting is essential in that the sponsor is responsible for informing the US Food and Drug Administration (FDA) and other regulatory authorities as well as all other participating Investigators of the event.

Under FDA ruling (US Code of Federal Regulations, Title 21 CFR Part 312.32) and the ICH Guidelines for Clinical Safety Data Management Definitions and Standards for Expedited Reporting, the sponsor is required to submit written documentation, in the form of a safety report, detailing:

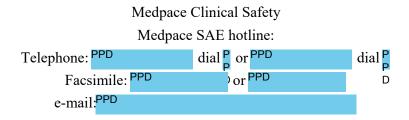
- Any event associated with the use of the drug, that is both serious and unexpected, or
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects, including reports of <u>mutagenicity</u>, <u>teratogenicity</u>, <u>or carcinogenicity</u>.

Written submission must be made by the sponsor to the FDA as soon as possible and in no event later than 15 calendar days after the sponsor's initial notification of the event. The sponsor shall also inform all Investigators.

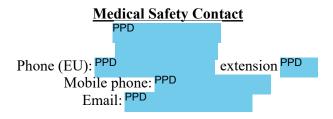
11.3.9.2 Time Frame for Reporting

Any death, SAE or pregnancy experienced by the subject after informed consent through the last study visit, regardless of relationship to study drug, , must be promptly reported (within 24 hours of the Investigator becoming aware of the event) by telephone or electronic transmission to the sponsor (or designee).

Contact information for **SAE** reporting:



Additionally, the Investigator will be able to contact the **Medical Monitor**:



11.3.9.3 Information to be Provided by the Investigator

SAEs must be recorded on the SAE form in the EDC system. This requirement includes all SAEs that occur after informed consent through the last study visit.

The minimum information required for SAE reporting includes identity of Investigator, site number, subject number, an event description, SAE term(s), onset date, the reason why the event is serious (i.e., the seriousness criteria) and the Investigator's assessment of the relationship of the event to study treatment. Additional SAE information including medications or other therapeutic measures used to treat the event, action taken with the study treatment due to the event, and the outcome/resolution of the event will be recorded. Paper forms for reporting SAEs will be provided to the study sites as back-up in case the EDC system is not accessible.

In all cases, the Investigator should continue to monitor the clinical situation and report all material facts relating to the progression or outcome of the SAE. Furthermore, the Investigator may be required to provide supplementary information as requested by Syntimmune or designee.

When reporting an SAE, the following additional points should be noted:

When the diagnosis of an SAE is known or suspected, the Investigator should report the
diagnosis or syndrome as the primary SAE term, rather than as signs or symptoms. Signs
and symptoms may then be described in the event description. For example, dyspnea
should not be used as an SAE term if the diagnosis, which caused the dyspnea, is known
to be malignant pleural effusion.

- Death should not be reported as an SAE, but as an outcome of a specific SAE, unless the event preceding the death is unknown. In the exceptional case where the events leading to death are unknown, then death may be used as an event term. If an autopsy was performed, the autopsy report should be provided.
- While most hospitalizations necessitate reporting of an SAE, some hospitalizations do not require SAE reporting, as follows:
 - Elective or previously scheduled surgery, e.g., a previously scheduled ventral hernia repair
 - Procedures for pre-existing conditions that have not worsened after initiation of treatment
 - Pre-specified study hospitalizations for observation
 - Events that result in hospital stays of less than 24 hours and that do not require admission, e.g., an emergency room visit for hematuria that results in a diagnosis of cystitis and discharge to home on oral antibiotics
- SAEs must, however, be reported for any surgical or procedural complication resulting in prolongation of the hospitalization.

11.3.10 Regulatory Reporting

Syntimmune (or designee) will process and evaluate all SAEs as soon as the reports are received. For each SAE received, Syntimmune will decide as to whether the criteria for expedited reporting have been met.

Syntimmune (or designee) will submit SAEs that meet the criteria for expedited reporting to the regulatory authorities in accordance with local regulations governing safety reporting. Reporting of SAEs by the Investigator to his or her IRB will be done in accordance with the standard operating procedures and policies of the IRB. Adequate documentation must be maintained showing that the IRB was properly notified.

11.3.11 Follow-up Information on a Serious Adverse Event (SAE)

Appropriate diagnostic tests should be performed and therapeutic measures, if indicated, should be instituted. Appropriate consultation and follow-up evaluations should be carried out until the event has returned to baseline or is otherwise explained by the Investigator.

If all required information on the SAE form is not available at the time of the initial report, follow-up information will be completed in the EDC system.

11.4 Other Safety Considerations

11.4.1 Laboratory Data

All laboratory data obtained during the study should be reviewed. Any abnormal value that leads to a change in subject management (e.g., requirement for additional medication or monitoring) or is of clinical significance by the Investigator should be reported as an AE and/or SAE as appropriate, unless this value is consistent with values obtained before entry into the study.

11.4.2 Medication Errors

Any medication error that results in an AE, even if it does not meet the definition of serious, requires reporting within 24 hours to the safety Medical Monitor.

11.4.3 Follow-Up of Adverse Events

Any SAE or AE assessed as related to study drug must be followed until either resolution of the event or determination by the Investigator that the event has become stable or irreversible. The Investigator will follow all drug related AEs until there is a return to the subject's baseline condition, or until a clinically satisfactory resolution has been achieved. The appropriate follow-up visits must be scheduled and the specific tests repeated or performed as necessary. The status of all AEs will be documented as of the last study visit.

Where a diagnosis is possible, it is preferable to report this diagnosis rather than a series of terms (signs/symptoms) relating to the diagnosis.

11.5 Safety Monitoring for Dose Escalation

Following dosing in each cohort, all safety/tolerability data (e.g., PEs, vital signs [including pulse oximetry], clinical safety laboratory tests, ECGs and AE/SAE assessments) as well as any available and relevant PD data collected through Day 42 will be reviewed by the DEC. A decision to escalate to the next cohort will be made. The recommendation may be to continue to

the next scheduled dose level, discontinue the study or to modify dosing to a dose less than the current dose or higher than the current dose but lower than the next planned dose.

12 STATISTICAL CONSIDERATIONS

All descriptive and inferential statistical analyses will be performed using the most recently released and available Statistical Analysis System (SAS) software, unless otherwise noted. Missing data will not be imputed unless otherwise stated. All clinical data captured will be provided in data listings. A Statistical Analysis Plan (SAP) and a Pharmacokinetic Analysis Plan (PAP) will be finalized prior to database lock.

12.1 General Design

All data for enrolled subjects will be presented in data listings by subject number.

Continuous data will be described using descriptive statistics: number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Frequencies and percentages will be used for summarizing discrete (categorical) data. When categorical data are presented, the percent will be suppressed when the count is zero to draw attention to the non-zero counts. The denominator for all percentages, unless otherwise specified, will be the number of subjects in the specified analysis population.

12.2 Sample Size Justification

Formal sample size calculations were not performed. The number of subjects was chosen based on feasibility and was considered sufficient to meet the study objectives.

12.3 Statistical Considerations

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP). The SAP may modify the plans outlined in the protocol; any deviations from the previously described statistical plan will be described and justified in an SAP amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate and will be described in the SAP. Methods of handling of missing data for different endpoints will be further specified in the SAP. In general, where individual data points are missing because of insufficient samples, dropouts, or other reasons, the data will be analyzed based on reduced denominators unless specified otherwise in the SAP.

Results will be summarized by cohorts.

12.3.1 Study Populations

Three populations will be employed in the analysis of study data:

• The **intent-to-treat (ITT)** population will consist of all subjects who have received at least one dose of study drug. All safety analyses will be performed on the ITT population.

- The **PK** population will consist of all subjects who receive at least one dose of study drug and have sufficient post-dose blood samples to obtain PK parameters.
- The **PD** population will consist of all subjects who receive at least one dose of study drug and have post-dose PD data available.

Primary safety analyses will be performed on the ITT population. Demographics, subject disposition, and screening and baseline characteristics will be summarized for the ITT, PK, and PD populations, where appropriate.

12.3.2 Subject Accountability, Demographics, and Baseline Characteristics

Subject disposition, demographic information and baseline characteristics will be presented. Any discrepancy between treatment to be given and treatment received will be accounted for in these displays.

12.3.3 Concomitant Medications

Concomitant medications will be coded using WHO Drug Dictionary (WHO-DD March 2013, Type B2 or later) and the data will be summarized and presented in tables and listings.

12.4 Planned PK Analysis

Study drug concentrations will be used to calculate the following PK parameters: $t_{1/2}$, C_{max} , T_{max} , and AUC_{0-24} and $AUC_{0-\infty}$. PK parameters will be determined using noncompartmental method(s). Descriptive statistics of PK parameters for SYNT001 will include mean, SD, coefficient of variation (CV), median, minimum, and maximum. T_{max} will be reported as median and range. All descriptive statistics will be performed on untransformed PK parameters and after log_{10} transformation of PK parameters.

For calculation of mean concentrations and generation of mean concentration-time profiles, all below the limit of quantification (BLQ) values will be set to zero except when an individual BLQ falls between 2 quantifiable values, in which case it will be omitted.

If there are values above the BLQ, but too sparse to allow full analysis, descriptive statistics will be performed on available values.

12.5 Safety Data

Safety observations and measurements include AEs, safety laboratory tests, vital sign measurements, PEs, and ECGs.

Treatment-emergent AEs will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA®; Version 19 or higher) System Organ Class (SOC) and preferred term, classified from verbatim terms. The incidence and percentage of subjects with at least 1 occurrence of a preferred term will be included, using the most severe grade. The number of events per preferred term will also be summarized. Causality (relationship to study treatment) will be summarized separately.

AEs, SAEs, and AEs leading to withdrawal, dose modification, or treatment discontinuation will be listed by subject, cohort, and overall per SOC and preferred terms. Duration of AEs will be determined and included in listings, along with action taken and outcome.

Laboratory results will be summarized by cohort. Incidence of laboratory abnormalities will be summarized. The worst on-study grade after the first dose of study drug will be summarized. Results for variables that are not coded will be presented in the listings as below, within, and above the normal limits of the local laboratory.

Vital sign measurements and change from baseline will be summarized at each scheduled time point by cohort using descriptive statistics.

Arithmetic mean of parameters from triplicate ECG will be calculated first for each participant at each planned time point. Then summary statistics of ECG test parameters (mean of triplicate) and change from baseline to each post-dose time point will be calculated. Shift tables for ECG test result category change (normal, abnormal, clinically abnormal) from pre-dose to each post-dose time point showing number and percentage of subjects with movement between categories will be presented by treatment group. Frequency and percentage of subjects experiencing potential QTc prolongation (QTcF > 450) will be summarized at each time point by cohort.

12.6 Pharmacodynamic/Activity Data

PD results will be summarized by cohort.

12.7 Immunogenicity Data

Immunogenicity results will be summarized by cohort.

12.8 Interim Analysis

No interim analysis is planned. Safety results will be examined for making dose-escalation decisions; no statistical analyses are planned for aiding these dose-escalation decisions.

13 DATA QUALITY ASSURANCE

All data will be entered in a validated electronic data capture system using single data entry. Standard procedures (including following data review guidelines, manual clinical review based on subject profiles, computerized validation to produce queries, and maintenance of an audit file which includes all database modifications) will be followed to ensure accurate data. Clinical personnel will review all data listings for outliers, data inconsistencies, and spelling errors.

During the study, a study site monitor will make site visits to review protocol compliance, compare electronic case report forms (eCRFs) against individual subject medical records, assess drug accountability, and ensure that the study is being conducted using pertinent regulatory requirements. eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that subject confidentiality is maintained. Checking the eCRFs for completeness, clarity and cross checking with source documents is required to monitor the progress of the study. Direct access to source data is also required for inspections and audits, and will be carried out giving due consideration to data protection and medical confidentiality. Each Investigator will have assured Syntimmune of full access to complete source data for study participants and associated necessary support at all times.

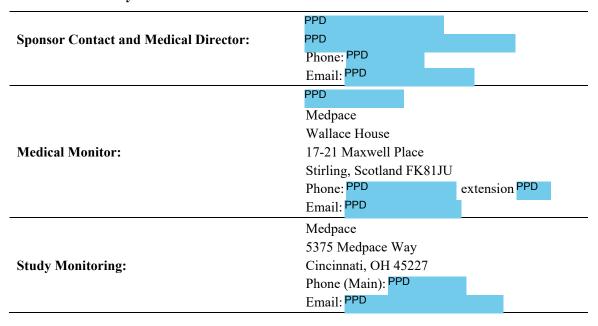
In addition to routine monitoring procedures, audits of clinical research activities in accordance with standard operating procedures (SOPs) may be performed to evaluate compliance with the principles of GCP. A regulatory authority may also wish to conduct an inspection (during the study or even after its completion). If a regulatory authority requests an inspection, the Investigator must immediately inform Syntimmune that this request has been made. Study conduct may be assessed during the study by a Clinical Quality Assurance representative(s) to ensure that the study is conducted in compliance with the protocol. This designee, as well as the site monitor, will be permitted to inspect the study documents (study protocol, eCRFs, investigational product accountability, original study-relevant medical records). All subject data will be treated confidentially. During the clinical study, access will be available to Syntimmune or their designee (e.g., contract research organization [CRO]) to view the eCRFs after completion of the individual sections of the study. Furthermore, the study protocol, each step of the data-recording procedure and the handling of the data as well as the study report may be subject to independent review by a Quality Assurance representative. Clinical site and study audits will be conducted as necessary to assure the validity of the study data.

14 STUDY ADMINISTRATION

14.1 Study Administrative Structure

The study administration structure is provided in Table 6.

Table 6: Study Administrative Structure



14.2 Ethical Conduct of the Study

The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH E6 Tripartite Guideline (January 1997), and in general, be conducted in a manner consistent with the principles described in the Declaration of Helsinki. The Investigator will ensure that the conduct of the study complies with the basic principles of GCP as outlined in the current version of 21 CFR, subpart D, Part 312, "Responsibilities of Sponsors and Investigators", Part 50, "Protection of Human Subjects", and Part 56, "Institutional Review Boards".

14.3 Informed Consent (ICF)

A properly executed, written informed consent document, in compliance with 21 CFR, Part 50 and the ICH guidelines, will be obtained from each subject before the subject is entered into the study and before any study screening procedure is performed that involves risk. Attention will be directed to the basic elements required for incorporation into the informed consent under US Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a]) and (21 CFR 50.25[b]), as necessary.

Sample ICFs will be supplied to each site. Syntimmune or its designee must review any proposed deviations from the sample ICF. The final IRB-approved document must be provided to Syntimmune for regulatory purposes.

It is the responsibility of the Investigator, or a person designated by the Investigator, to obtain written informed consent from each subject (or the subject's legally authorized representative) participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. In the case where the subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the subject has orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. A copy of the ICF must be provided to the subject or to the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

The eCRF for this study contains a section for documenting informed subject consent, and this must be completed appropriately. Signed ICFs must remain in each subject's study file and must be available for verification by site monitors at any time. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated as necessary. All subjects (including those already being treated) should be informed of the new information, should be given a copy of the revised form, and should give their consent to continue in the study.

14.4 Institutional Review Board

This study is being conducted under US IND 128152. This protocol (and any modifications) and appropriate consent procedures must be reviewed and approved by an IRB. This board must operate in accordance with the current federal or local regulations. The Investigator will send a letter or certificate of IRB approval to Syntimmune (or designee) before subject enrollment and whenever subsequent modifications to the protocol are made.

14.5 Dose Escalation Committee

The DEC will be responsible for confirming the safety of the investigative product prior to dose escalation, as well as the dose level for each successive cohort. In addition, over the course of the study, the DEC will review any drug-related SAEs to determine if modifications to the study or other measures are necessary to ensure the safety of the subjects. The DEC will consist of the Medical Monitor, an Independent Clinical Expert and a Syntimmune Medical Officer. To

assist in the safety assessments, the DEC may request that Investigators, other experts, or members within their organizations review the data and participate in the discussions.

14.6 Future Use of Subject Samples

Not all the tissue and blood components obtained during this study may be required for the tests that are part of the clinical trial. Available samples may be used for additional research. This research will help to understand disease subtypes, drug response and AE, and possibly identify new drug targets or biomarkers that predict subject response to treatment. The use of the samples for internal research will be done using the guidelines defined by the FDA guidance for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individual Identifiable (issued 25 April 2006) and the European Medicines Agency (EMA) Reflection Paper on Pharmacogenetic Samples, Testing and Data Handling (Doc. Ref.

EMEA/CHMP/PGxWP/201914/2006; 15 November 2007). If a subject requests destruction of their tissue and blood samples and the samples have not yet been de-identified, Syntimmune will destroy the samples as described in this FDA guidance. Syntimmune will notify the Investigator in writing that the samples have been destroyed.

15 CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications to ongoing studies must be made only after consultation between a Syntimmune representative and the Investigator. Protocol modifications will be prepared, reviewed, and approved by Syntimmune representatives.

All protocol modifications must be submitted to the IRB for information and approval in accordance with local requirements, and to regulatory agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study subjects, or when the change involves only logistical or administrative aspects of the trial (e.g., change in site monitor, change of telephone number).

16 CONDITIONS FOR TERMINATING THE STUDY

Syntimmune has the right to terminate the study at any time. In terminating the study, Syntimmune and the Investigator will ensure that adequate consideration is given to the protection of the subjects' interests.

17 STUDY DOCUMENTATION, CRFS, AND RECORD KEEPING

17.1 Investigator's Files and Retention of Documents

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into 2 separate categories as follows: (1) Investigator's study file and (2) subject clinical source documents.

The Investigator's study file will contain the protocol and protocol amendments, eCRFs, query forms, IRB and governmental approval with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Subject clinical source documents (usually predefined by the project to record key efficacy and safety parameters independent of the eCRFs) may include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalogram, X-ray, pathology and special assessment reports, signed ICFs, consultant letters, and subject screening and enrollment logs. The Investigator must keep these 2 categories of documents on file for at least 2 years following the marketing application approval date for the study treatment and for the indication being investigated or for 2 years after the development program is discontinued and the FDA notified. After that period, the documents may be destroyed subject to local regulations with prior written permission from Syntimmune. If the Investigator wants to assign the study records to another party or move them to another location, Syntimmune must be notified in advance.

If the Investigator cannot guarantee the archiving requirement at the study site for any or all of the documents, special arrangements must be made between the Investigator and Syntimmune to store these in a sealed container outside of the study site so that they can be returned sealed to the Investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the study site.

17.2 Source Documents and Background Data

Investigators must maintain adequate and accurate source documents on which the eCRFs for each subject are based. They are separate and distinct from the eCRFs.

These records include detailed notes on the following:

- Medical history
- Date and time of informed consent with Health Insurance Portability and Accountability
 Act (HIPAA) authorization either contained in the ICF or presented to the subject
 candidate as a standalone document
- Description of the complete consenting process
- The basic identifying information that linked the subject's medical record with the eCRFs
- The results of all diagnostic tests performed, diagnoses made, therapy provided, and any other data on the condition of the subject
- The medical condition of the subject during their involvement in the study
- All AEs
- The subject's exposure to the study medication
- The subject's exposure to any concomitant therapy
- All relevant observations and data on the condition of the subject throughout the trial
- Justification for all entries in the subject's eCRF

A subject log of all potentially eligible subjects considered, but not consented, for obvious deviations from the entry criteria, will be kept at each site. The log will contain subjects' initials, diagnosis, eligibility, or, if not eligible, reason for not consenting. All consented subjects will be logged, regardless of whether they ultimately enroll.

Upon request, the Investigator will supply Syntimmune with any required background data from the study documentation or clinic records. This is particularly important when eCRFs are illegible or when errors in data transcription are suspected. In case of special problems or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

17.3 Audits and Inspections

The Investigator should understand that source documents for this study should be made available to appropriately qualified personnel from Syntimmune (or designee), or to health authority inspectors after appropriate notification. The verification of the eCRF data must be by direct inspection of source documents.

17.4 Electronic Case Report Forms

Clinical trial data for this study will be captured on eCRF designed for computer processing and analysis. This computerized system will be validated and compliant with 21 CFR Part 11. Corrections to data will be made using 21 CFR Part 11, Electronic Records; Electronic Signatures. If corrections are made after review and sign-off by the Investigator, he/she must be aware of the changes and provide written acknowledgement. There will also be an electronic audit trail. Corrections on paper CRFs must be initialed and dated by the person making the change. The Investigator agrees to provide all information requested on the eCRF in an accurate manner using instructions provided. The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to Syntimmune in the eCRF and in all required reports.

An eCRF is required to be submitted for every subject who receives any amount of study drug. This includes submission of retrievable data on subjects who withdraw before completion of the study. Prior to submission, eCRFs must be reviewed for completeness and accuracy, and signed and dated where either indicated, by the Principal Investigator or authorized delegate from the study staff. If a subject stops treatment or terminates from the study, the dates and reasons must be noted on the eCRF.

18 MONITORING THE STUDY

It is understood that the responsible Syntimmune site monitor (or designee) will contact and visit the Investigator regularly and will be allowed on request to inspect the various records of the trial (eCRFs and other pertinent data) if subject confidentiality is maintained in accordance with local requirements.

It will be the site monitor's responsibility to inspect the eCRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The site monitor should have access to laboratory test reports and other subject records needed to verify the entries on the eCRF. The Investigator (or designee) must agree to cooperate with the site monitor to ensure that any problems detected during these monitoring visits are resolved.

19 CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The Investigator must ensure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On eCRFs or other documents submitted to Syntimmune, subjects should be identified by an identification code and not by their names. The Investigator should keep a subject enrollment log showing codes, names, and addresses. The Investigator should maintain documents not for submission to Syntimmune (e.g., subjects' written consent forms) in strict confidence.

Authorized regulatory officials and Syntimmune personnel (or their representatives) will be allowed full access to inspect and copy the records. All study drugs, subject bodily fluids and tissue, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by Syntimmune.

The Principal Investigator also agrees that all information received from Syntimmune, including but not limited to the IB, this protocol, eCRFs, the INDs, and any other study information remain the sole and exclusive property of Syntimmune during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The Principal Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

20 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. The Investigator agrees that any manuscript or abstract they author may be published only after receiving written permission from Syntimmune.

If Syntimmune coordinates a publication or presentation of study results from all study sites, the participation of Investigator or other representatives of study site as a named author shall be determined in accordance with Syntimmune policy and generally accepted standards for authorship.

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Appendix A: NCI CTCAE, Version 4.03

Common Terminology Criteria for Adverse Events (CTCAE)

Version 4.0

Published: May 28, 2009 (v4.03: June 14, 2010)

U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health National Cancer Institute

Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

Publish Date: May 28, 2009

Quick Reference

The NCI Common Terminology Criteria for Adverse Events is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

SOC

System Organ Class, the highest level of the MedDRA hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e.g., SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

CTCAE Terms

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may <u>not</u> be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v4.0 term is a MedDRA LLT (Lowest Level Term).

Definitions

A brief definition is provided to clarify the meaning of each AE term.

Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

A Semi-colon indicates 'or' within the description of the grade.

A single dash (-) indicates a grade is not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

[†] CTCAE v4.0 incorporates certain elements of the MedDRA terminology. For further details on MedDRA refer to the MedDRA MSSO Web site (http://www.meddramsso.com).

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	В	lood and lymphatic syste			
			Grade	I	1
Adverse Event	1	2	3	4	5
nemia	Hemoglobin (Hgb) <lln -="" 10.0<br="">g/dL; <lln -="" -<br="" 6.2="" <lln="" l;="" mmol="">100 g/L</lln></lln>	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
	ed by an reduction in the amount of palpitations of the heart, soft syst	•	• • •	ay include pallor of the skin and m	nucous
Bone marrow hypocellular	Mildly hypocellular or <=25% reduction from normal cellularity for age	Moderately hypocellular or >25 - <50% reduction from normal cellularity for age	Severely hypocellular or >50 - <=75% reduction cellularity from normal for age	Aplastic persistent for longer than 2 weeks	Death
Definition: A disorder characteriz	ed by the inability of the bone mar	row to produce hematopoietic eler	ments.		
Disseminated intravascular coagulation	-	Laboratory findings with no bleeding	Laboratory findings and bleeding	Life-threatening consequences; urgent intervention indicated	Death
	ed by systemic pathological activa s depleted of platelets and coagula	-	which results in clot formation thro	oughout the body. There is an incr	ease in the
Febrile neutropenia	-	-	ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour.	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz degrees F) for more than one ho	ed by an ANC <1000/mm3 and a sur.	single temperature of >38.3 degre	es C (101 degrees F) or a sustaine	ed temperature of >=38 degrees 0	C (100.4
Hemolysis	Laboratory evidence of hemolysis only (e.g., direct antiglobulin test; DAT; Coombs'; schistocytes; decreased haptoglobin)	Evidence of hemolysis and >=2 gm decrease in hemoglobin.	Transfusion or medical intervention indicated (e.g., steroids)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by laboratory test results that in	ndicate widespread erythrocyte ce	Il membrane destruction.		
Hemolytic uremic syndrome	Evidence of RBC destruction (schistocytosis) without clinical consequences	-	Laboratory findings with clinical consequences (e.g., renal insufficiency, petechiae)	Life-threatening consequences, (e.g., CNS hemorrhage or thrombosis/embolism or renal failure)	Death
Definition: A disorder characteriz	ed by a form of thrombotic microal	ngiopathy with renal failure, hemo	lytic anemia, and severe thromboo	ytopenia.	
Leukocytosis	-	-	>100,000/mm3	Clinical manifestations of leucostasis; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by laboratory test results that ir	ndicate an increased number of wl	nite blood cells in the blood.	•	
Lymph node pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by a sensation of marked disco	mfort in a lymph node.			
Spleen disorder	Incidental findings (e.g., Howell- Jolly bodies); mild degree of thrombocytosis and leukocytosis	Prophylactic antibiotics indicated	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder of the splee	en.				
Thrombotic thrombocytopenic ourpura	Evidence of RBC destruction (schistocytosis) without clinical consequences	-	Laboratory findings with clinical consequences (e.g., renal insufficiency, petechiae)	Life-threatening consequences, (e.g., CNS hemorrhage or thrombosis/embolism or renal failure)	Death
	ed by the presence of microangion	•	cytopenic purpura, fever, renal abr	normalities and neurological abnor	malities suc
as seizures, hemiplegia, and visu	ual disturbances. It is an acute or s	subacute condition.	T	I	
Blood and lymphatic system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

		Cardiac disorde			
		T	Grade	T	
Adverse Event	1	2	3	4	5
Acute coronary syndrome	-	Symptomatic, progressive angina; cardiac enzymes normal; hemodynamically stable	Symptomatic, unstable angina and/or acute myocardial infarction, cardiac enzymes abnormal, hemodynamically stable	Symptomatic, unstable angina and/or acute myocardial infarction, cardiac enzymes abnormal, hemodynamically unstable	Death
	ed by signs and symptoms related unstable angina to myocardial infa	I to acute ischemia of the myocard arction.	lium secondary to coronary artery	disease. The clinical presentation	covers a
Aortic valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis by imaging	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death
Definition: A disorder characterize	ed by a defect in aortic valve funct	tion or structure.			
Asystole	Periods of asystole; non-urgent medical management indicated	-	-	Life-threatening consequences; urgent intervention indicated	Death
		ac electrical activity. Typically, this			
Atrial fibrillation	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker), or ablation	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize originates above the ventricles.	ed by a dysrhythmia without disce	rnible P waves and an irregular ve	entricular response due to multiple	reentry circuits. The rhythm distur	bance
Atrial flutter	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker), or ablation	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterizatria.	ed by a dysrhythmia with organize	ed rhythmic atrial contractions with	a rate of 200-300 beats per minut	e. The rhythm disturbance origina	tes in the
Atrioventricular block complete	-	Non-urgent intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by a dysrhythmia with complete	e failure of atrial electrical impulse	conduction through the AV node t	to the ventricles.	•
Atrioventricular block first degree	Asymptomatic, intervention not indicated	Non-urgent intervention indicated	-	-	-
	ed by a dysrhythmia with a delay i interval greater than 200 milliseco	in the time required for the conduction	tion of an electrical impulse throuç	gh the atrioventricular (AV) node b	eyond 0.2
Cardiac arrest	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by cessation of the pumping fu	nction of the heart.	<u> </u>	<u> </u>	
Chest pain - cardiac	Mild pain	Moderate pain; limiting instrumental ADL	Pain at rest; limiting self care ADL	-	-
Definition: A disorder characterize	ed by substernal discomfort due to	o insufficient myocardial oxygenati	on.		
Conduction disorder	Mild symptoms; intervention not indicated	Moderate symptoms	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by pathological irregularities in	the cardiac conduction system.			
Constrictive pericarditis	-	-	Symptomatic heart failure or other cardiac symptoms, responsive to intervention	Refractory heart failure or other poorly controlled cardiac symptoms	Death
Definition: A disorder characterize	ed by a thickened and fibrotic peri	। cardial sac; these fibrotic changes	1 '	1	e action.
Heart failure	Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging	Symptoms with mild to moderate activity or exertion	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic	Death

		Cardiac disorde	ers		
			Grade		
Adverse Event	1	2	3	4	5
Left ventricular systolic dysfunction	-		Symptomatic due to drop in ejection fraction responsive to intervention	Refractory or poorly controlled heart failure due to drop in ejection fraction; intervention such as ventricular assist device, intravenous vasopressor support, or heart transplant indicated	Death
	ed by failure of the left ventricle to nea, orthopnea, and other signs ar		an increase in distending pressure at an increase in distending pressure and edema.	e and in end-diastolic volume. Clin	nical
Mitral valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis by imaging	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death
Definition: A disorder characteriz	ed by a defect in mitral valve funct	ion or structure.			
Mobitz (type) II atrioventricular block	Asymptomatic, intervention not indicated	Symptomatic; medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening consequences; urgent intervention indicated	Death
	ed by a dysrhythmia with relatively atrioventricular (AV) node to the ve	•	block of an atrial impulse. This is t	he result of intermittent failure of a	trial electrica
Mobitz type I	Asymptomatic, intervention not indicated	Symptomatic; medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening consequences; urgent intervention indicated	Death
	ed by a dysrhythmia with a progre on through the atrioventricular (AV		ior to the blocking of an atrial impu	llse. This is the result of intermitter	nt failure of
Myocardial infarction	-	Asymptomatic and cardiac enzymes minimally abnormal and no evidence of ischemic ECG changes	Severe symptoms; cardiac enzymes abnormal; hemodynamically stable; ECG changes consistent with infarction	Life-threatening consequences; hemodynamically unstable	Death
Definition: A disorder characteriz	ed by gross necrosis of the myoca	rdium; this is due to an interruptio	on of blood supply to the area.		
Myocarditis	Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	Death
Definition: A disorder characteriz	ed by inflammation of the muscle	tissue of the heart.			
Palpitations	Mild symptoms; intervention not indicated	Intervention indicated	-	-	-
Definition: A disorder characteriz	ed by an unpleasant sensation of	irregular and/or forceful beating of	f the heart.		
Paroxysmal atrial tachycardia	Asymptomatic, intervention not indicated	Symptomatic; medical management indicated	IV medication indicated	Life-threatening consequences; incompletely controlled medically; cardioversion indicated	Death
Definition: A disorder characteriz originates in the atria.	ed by a dysrhythmia with abrupt o	nset and sudden termination of at	rial contractions with a rate of 150-	-250 beats per minute. The rhythm	n disturbance
Pericardial effusion	-	Asymptomatic effusion size small to moderate	Effusion with physiologic consequences	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by fluid collection within the pe	ricardial sac, usually due to inflam	mation.		
Pericardial tamponade	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by an increase in intrapericardi	al pressure due to the collection o	of blood or fluid in the pericardium.	ı	
Pericarditis	Asymptomatic, ECG or physical findings (e.g., rub) consistent with pericarditis	Symptomatic pericarditis (e.g., chest pain)	Pericarditis with physiologic consequences (e.g., pericardial constriction)	Life-threatening consequences; urgent intervention indicated	Death
D 6 ''' A 1''	ad by irritation to the layers of the	pericardium (the protective sac ar	cound the heart)	•	•

	1	Cardiac disorde	ers		
			Grade		
Adverse Event	1	2	3	4	5
Pulmonary valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis by imaging	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death
Definition: A disorder characteriz	ed by a defect in pulmonary valve	function or structure.	Γ	T	1
Restrictive cardiomyopathy	-	-	Symptomatic heart failure or other cardiac symptoms, responsive to intervention	Refractory heart failure or other poorly controlled cardiac symptoms	Death
	ed by an inability of the ventricles				Ι
Right ventricular dysfunction	Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Severe symptoms, associated with hypoxemia, right heart failure; oxygen indicated	Life-threatening consequences; urgent intervention indicated (e.g., ventricular assist device); heart transplant indicated	Death
Definition: A disorder characteriz	ed by impairment of right ventricul	ar function associated with low eje	ection fraction and a decrease in m	notility of the right ventricular wall.	
Sick sinus syndrome	Asymptomatic, intervention not indicated	Non-urgent intervention indicated	Severe, medically significant; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	ed by a dysrhythmia with alternation				1
Sinus bradycardia	Asymptomatic, intervention not indicated	Symptomatic, medical intervention indicated	Severe, medically significant, medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by a dysrhythmia with a heart r		that originates in the sinus node.		
Sinus tachycardia	Asymptomatic, intervention not indicated	Symptomatic; non-urgent medical intervention indicated	Urgent medical intervention indicated	-	-
Definition: A disorder characteriz	ed by a dysrhythmia with a heart r	ate greater than 100 beats per mi	nute that originates in the sinus no	ode.	1
Supraventricular tachycardia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by a dysrhythmia with a heart r	ate greater than 100 beats per mi	nute that originates above the ven	tricles.	
Tricuspid valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death
	ed by a defect in tricuspid valve fu				
Ventricular arrhythmia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by a dysrhythmia that originate	s in the ventricles.	T	1	
Ventricular fibrillation	-	-	-	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Definition: A disorder characteriz ventricles.	ed by a dysrhythmia without disce	rnible QRS complexes due to rapi	d repetitive excitation of myocardi	al fibers without coordinated contr	action of the
Ventricular tachycardia	-	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by a dysrhythmia with a heart r	ate greater than 100 beats per mi	nute that originates distal to the bu	undle of His.	
Wolff-Parkinson-White syndrome	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with procedure	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by the presence of an accesso	ry conductive pathway between th	e atria and the ventricles that cau	ses premature ventricular activation	n.
Cardiac disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting ageappropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Congenital, familial and genetic disorders						
			Grade			
Adverse Event	1	2	3	4	5	
Congenital, familial and genetic	Asymptomatic or mild	Moderate; minimal, local or	Severe or medically significant	Life-threatening consequences;	Death	
disorders - Other, specify	symptoms; clinical or diagnostic	noninvasive intervention	but not immediately life-	urgent intervention indicated		
	observations only; intervention	indicated; limiting age-	threatening; hospitalization or			
	not indicated	appropriate instrumental ADL	prolongation of existing			
			hospitalization indicated;			
1			disabling; limiting self care ADL			

		Ear and labyrinth dis	orders		
		•	Grade		
Adverse Event	1	2	3	4	5
Ear pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by a sensation of marked disco	mfort in the ear.			
External ear inflammation	External otitis with erythema or dry desquamation	External otitis with moist desquamation, edema, enhanced cerumen or discharge; tympanic membrane perforation; tympanostomy	External otitis with mastoiditis; stenosis or osteomyelitis; necrosis of soft tissue or bone	Urgent operative intervention indicated	Death
Definition: A disorder characteriz	ed by inflammation, swelling and r	edness to the outer ear and ear ca	anal.		
External ear pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by a sensation of marked disco	mfort in the external ear region.			
Hearing impaired	Adults enrolled on a Monitoring Program (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift of 15 - 25 dB averaged at 2 contiguous test frequencies in at least one ear. Adults not enrolled in Monitoring Program: subjective change in hearing in the absence of documented hearing loss.	Adults enrolled in Monitoring Program (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift of >25 dB averaged at 2 contiguous test frequencies in at least one ear. Adults not enrolled in Monitoring Program: hearing loss but hearing aid or intervention not indicated; limiting instrumental ADL.	Adults enrolled in Monitoring Program (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift of >25 dB averaged at 3 contiguous test frequencies in at least one ear; therapeutic intervention indicated. Adults not enrolled in Monitoring Program: hearing loss with hearing aid or intervention indicated; limiting self care ADL.	Adults: Decrease in hearing to profound bilateral loss (absolute threshold >80 dB HL at 2 kHz and above); non-servicable hearing. Pediatric: Audiologic indication for cochlear implant and additional speech-language related services indicated.	-
	Pediatric (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift >20 dB at 8 kHz in at least one ear.	Pediatric (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift >20 dB at 4 kHz and above in at least one ear.	Pediatric (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): hearing loss sufficient to indicate therapeutic intervention, including hearing aids; threshold shift >20 dB at 3 kHz and above in at least one ear; additional speech-language related services indicated.		
	ed by partial or complete loss of th				I
Middle ear inflammation	Serous otitis	Serous otitis, medical intervention indicated	Mastoiditis; necrosis of canal soft tissue or bone	Life-threatening consequences; urgent intervention indicated	Death
	ed by inflammation (physiologic re				
Tinnitus Definition: A disorder observatoriz	Mild symptoms; intervention not indicated ed by noise in the ears, such as rir	instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Vertigo	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characteriz vertigo).	ed by a sensation as if the externa	ı	ı	he himself were revolving in space	e (subjective
Vestibular disorder	-	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by dizziness, imbalance, nause	ea, and vision problems.			
Ear and labyrinth disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

		Endocrine disord	lers		
			Grade		
Adverse Event	1	2	3	4	5
Adrenal insufficiency	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
	s when the adrenal cortex does not son's disease or primary adrenal ins		cortisol and in some cases, the no	ormone aldosterone. It may be due	to a disorder
Cushingoid	Mild symptoms; intervention not indicated		Severe symptoms, medical intervention or hospitalization indicated	-	-
Definition: A disorder characterion osteoporosis, usually due to exc	zed by signs and symptoms that re ogenous corticosteroids.	semble Cushing's disease or sync	Irome: buffalo hump obesity, striat	tions, adiposity, hypertension, diab	etes, and
Delayed puberty	-	No breast development by age 13 yrs for females; testes volume of <3 cc or no Tanner Stage 2 development by age 14.5 yrs for males	No breast development by age 14 yrs for females; no increase in testes volume or no Tanner Stage 2 by age 16 yrs for males; hormone replacement indicated	-	-
Definition: A disorder characteri	zed by unusually late sexual maturi	ity.			
Growth accelerated	-	>= +2 SD (standard deviation) above mid parental height or target height	-	-	-
Definition: A disorder characteri	zed by greater growth than expecte	ed for age.			
Hyperparathyroidism	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characteri the blood).	zed by an increase in production of	parathyroid hormone by the para	thyroid glands. This results in hype	ercalcemia (abnormally high levels	of calcium in
Hyperthyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteri	zed by excessive levels of thyroid h	normone in the body. Common car	uses include an overactive thyroid	gland or thyroid hormone overdos	se.
Hypoparathyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; medical intervention or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteri	zed by a decrease in production of	parathyroid hormone by the parat	hyroid glands.		
Hypothyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid replacement indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteri	zed by a decrease in production of	thyroid hormone by the thyroid gla	and.	ı	
Precocious puberty	Physical signs of puberty with no biochemical markers for females <8 years and males <9 years	Physical signs and biochemical markers of puberty for females <8 years and males <9 years	-	-	-
Definition: A disorder characteri 9 for boys.	zed by unusually early developmen	nt of secondary sexual features; th	e onset of sexual maturation begir	ns usually before age 8 for girls an	d before age
Virilization	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characteri	zed by inappropriate masculinization	on occurring in a female or prepub	ertal male.		
Endocrine disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Surred vision in transvertion not indicated programments and programments			Eye dis	sorders		
Definition: A disorder characterized by visual perception of underset of tazzy images. Symptomatic disorder of tazzy images. Symptomatic disorder of tazzy images. Symptomatic with marked disorders of tazzy images. Symptomatic with marked disorder disorders disorders of tazzy images. Symptomatic with marked disorders of tazzy images. Symptomatic with marked disorders of tazzy images. Symptomatic with with with with with with with with				Grade		
Definition: A disorder characterized by visual perception of invalence of history of the properties of the control of the properties of	Adverse Event	1	2	3	4	5
Castacid Apyrophorensic clinical or disponent contentions only indicated agrouption for indicated and agrouption for indicated properties and agrouption on the indicated and agrouption for indicated and agrouption on the indicated and agrouption of the correct properties agrouption agroup agrouption a			instrumental ADL	Limiting self care ADL	-	-
diagnostic observations only inferention not indicated all grounds of the complete opacity of the crystalline forms of ornor or both eyes. This results in a decrease in visual acuity and eventual blindness if untreased. Definition: A disorder characterized by partial or complete opacity of the crystalline forms of ornor or both eyes. This results in a decrease in visual acuity and eventual blindness if untreased. Compunctivitis Asymptomatic or mild symptoms: intervention not indicated (e.g., proposatic ornal proposation) intervention indicated (e.g., proposatic		1		1	I	I
Definition: A disorder characterized by a narea of epithelial tissue loss on the surface of the conjunctive of the eye. Comeal ulcer - Symptomatic, inclinated or substance of epithelial tissue loss on the surface of the connection of disorder characterized by inflammation, seeling and referenses to the conjunctive of the eye. Comeal ulcer - Symptomatic, inclinated (e.g., and referenses to the conjunctive of the eye. Comeal ulcer - Symptomatic, immiding and referenses to the conjunctive of the eye. Comeal ulcer - Symptomatic, immiding and referenses to the conjunctive of the eye. Comeal ulcer - Symptomatic, immiding and referenses to the conjunctive of the eye. Definition: A disorder characterized by an area of epithelial tissue loss on the surface of the cornea. It is associated with inflammatory cells in the cornea and anterior charabor. Definition: A disorder characterized by dynees of the comea and conjunctive. Extraocular muscle paresis Asymptomatic, clinical or diagnostic observations only instrumental ADL. Definition: A disorder characterized by incompile paralysis of an exhapocular muscle. Experimental or disorder characterized by a sensation of marked december of the eye. Eyelid function disorder Asymptomatic, clinical or diagnostic observations only instrumental ADL. Definition: A disorder characterized by a sensation of marked december of the eye. Eyelid function disorder Asymptomatic, clinical or diagnostic observations only instrumental ADL. Definition: A disorder characterized by a minimal paralysis of an exhapocular muscle. Eyelid function disorder Asymptomatic, clinical or diagnostic observations only instrumental ADL. Definition: A disorder characterized by an individual seeing spots before their eyes. The spots are a shadow of opaque cell fragments in the vitrous humor or lons. EICIP Causing early visual paralysis of an exhapocular	Cataract	diagnostic observations only;	decrease in visual acuity	decrease in visual acuity (worse than 20/40 but better than 20/200); operative intervention indicated (e.g.,	, ,	-
Asymptomatic or mild indicated (a.g., proposal control indicated (b.g.,		I erized by partial or complete op	I acity of the crystalline lens of c		I n a decrease in visual acuity an	I d eventual blindness if
Symptomatic; medical intervention indicated (e.g., techning self care ADL; declining vision (worse than 1 (20/200 or worse) in the 20/200 or worse)		symptoms; intervention not	intervention indicated (e.g., antibiotics); limiting	Limiting self care ADL	-	-
Intervention indicated (e.g., apolical agents); imiting instrumental ADL Definition: A disorder characterized by an area of epithelial tissue loss on the surface of the cornea. It is associated with inflammatory cells in the cornea and anterior chamber.	Definition: A disorder characte	erized by inflammation, swelling	and redness to the conjunctiv	a of the eye.		
Dry eye Asymptomatic; clinical or diagnostic observations only; mild symptoms relieved by lubricants Definition: A disorder characterized by dryness of the comea and conjunctiva. Extraocular muscle paresis Asymptomatic; clinical or diagnostic observations only; more diagnostic observations o	Corneal ulcer	-	intervention indicated (e.g., topical agents); limiting	declining vision (worse than	(20/200 or worse) in the	-
diagnostic observations only; mild symptoms relieve du by lubricants Definition: A disorder characterized by dryness of the cornea and conjunctiva. Extracocular muscle paresis Asymptomatic; clinical or diagnostic observations only instrumental ADL Definition: A disorder characterized by incomplete paralysis of an extraccular muscle. Eye pain Mild pain Moderate pain; limiting instrumental ADL Definition: A disorder characterized by a sensation of marked discomfort in the eye. Eyelid function disorder diagnostic observations only; instrumental ADL Definition: A disorder characterized by a sensation of marked discomfort in the eye. Eyelid function disorder diagnostic observations only; instrumental ADL Definition: A disorder characterized by a sensation of marked discomfort in the eye. Eyelid function disorder diagnostic observations only; instrumental ADL Definition: A disorder characterized by impaired eyelid function. Flinahing lights Symptomatic but not limiting Land ADL Definition: A disorder characterized by a sudden or brief burst of light. Eloaters ADL Definition: A disorder characterized by an individual seeing spots before their eyes. The spots are shadows of opaque cell fragments in the vitreous humor or lens. Elova cate individual seeing spots before their eyes. The spots are shadows of opaque cell fragments in the vitreous humor or lens. Elova cate indicated; limiting self care ADL or oral agents indicated; limiting self care ADL Definition: A disorder characterized by an increase in pressure in the eyeball due to obstruction of the aqueous humor outlow. EloPacual agents; limiting self care ADL Definition: A disorder characterized by inflammation to the come of the eye. Night blindness Symptomatic but not limiting limitument	Definition: A disorder characte	erized by an area of epithelial ti	ssue loss on the surface of the	cornea. It is associated with in	flammatory cells in the cornea	and anterior chamber.
Extraocular muscle paresis	Dry eye	diagnostic observations only; mild symptoms relieved by	agents indicated; limiting	(<20/40); limiting self care	-	-
Definition: A disorder characterized by incomplete paralysis of an extraocular muscle. Eye pain Mild pain Moderate pain; limiting care ADL Definition: A disorder characterized by a sensation of marked discomfort in the eye. Eyelid function disorder Asymptomatic; clinical or diagnostic observations only; intervention indicated; intervention on indicated por paralysis of a supplemental ADL Definition: A disorder characterized by impaired eyelid function. Flashing lights Symptomatic but not limiting ADL Definition: A disorder characterized by a sudden or brief bust of light. Floaters Symptomatic but not limiting IL limiting instrumental ADL Definition: A disorder characterized by a nicrease in pressure in the eyeball due to obstruction indicated; limiting instrumental ADL Definition: A disorder characterized by an increase in pressure in the eyeball due to obstruction of the aqueous humor outflow. Definition: A disorder characterized by an increase in pressure in the eyeball due to obstruction of the aqueous humor outflow. Event the eye. Definition: A disorder characterized by an increase in pressure in the eyeball due to obstruction of the aqueous humor outflow. Event the eyeball due to obstruction of the aqueous humor outflow. Event the eyeball due to obstruction of the aqueous humor outflow. Definition: A disorder characterized by an increase in pressure in the eyeball due to obstruction of the aqueous humor outflow. Event the eyeball due to obstruction of the aqueous humor outflow. Event the eyeball due to obstruction of the aqueous humor outflow. Definition: A disorder characterized by inflammation to the cornea of the eye. Event the eyeball due to obstruction of the aqueous humor outflow. Event the eyeball due to obstruction of the aqueous humor outflow. Event the eyeball due to obstruction of the aqueous humor outflow. Event the eyeball due to obstruction of the aqueous humor outflow. Event the eyeball due to obstruction of the aqueous humor outflow. Event the eyeball due to obstruct	Definition: A disorder characte	erized by dryness of the cornea	and conjunctiva.		•	•
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Instrumental ADL Care ADL Care ADL	Definition: A disorder characte	erized by incomplete paralysis	of an extraocular muscle.		Г	т
Eyelid function disorder Asymptomatic; clinical or diagnostic observations only; intervention not indicated intervention indicated; limiting instrumental ADL Definition: A disorder characterized by impaired eyelid function. Flashing lights Symptomatic but not limiting ADL Definition: A disorder characterized by a sudden or brief burst of light. Floaters Symptomatic but not limiting ADL Definition: A disorder characterized by an individual seeing spots before their eyes. The spots are shadows of opaque cell fragments in the vitreous humor or lens. Glaucoma Elevated intraocular pressure (EIOP) with single topical agent for intervention; no visual field deficit no visual field deficit Floaters Symptomatic but not limiting ADL Elevated intraocular pressure (EIOP) with single topical agent for intervention; no visual field deficits, multiple topical intervention indicated; limiting afficace ADL Definition: A disorder characterized by an increase in pressure in the eyeball due to obstruction of the aqueous humor outlow. Keratitis - Symptomatic: medical intervention indicated (e.g., topical agents); limiting self care ADL Definition: A disorder characterized by inflammation to the correa of the eye. Night blindness Symptomatic but not limiting Limiting instrumental ADL Limiting self care ADL Simiting self care ADL Blindness (20/200 or worse) in the affected eye affected eye affected eye affected eye Limiting self care ADL Definition: A disorder characterized by inflammation to the correa of the eye. Night blindness Symptomatic but not limiting Limiting instrumental ADL Limiting self care ADL Limiting self care ADL Blindness (20/200 or worse) in the affected eye affected eye Limiting self care ADL Blindness (20/200 or worse) in the affected eye ADL Limiting self care ADL Blindness (20/200 or worse) in the affected eye ADL Limiting self care ADL Limiting ins	Eye pain	Mild pain			-	-
diagnostic observations only, intervention not indicated; limiting instrumental ADL Definition: A disorder characterized by impaired eyelid function. Flashing lights Symptomatic but not limiting ADL Limiting instrumental ADL Limiting self care ADL	Definition: A disorder characte	erized by a sensation of marked	d discomfort in the eye.	1	1	1
Flashing lights	Eyelid function disorder	diagnostic observations only;	intervention indicated;	operative intervention	-	-
Definition: A disorder characterized by a sudden or brief burst of light. Floaters Symptomatic but not limiting ADL Definition: A disorder characterized by an individual seeing spots before their eyes. The spots are shadows of opaque cell fragments in the vitreous humor or lens. Elevated intraocular pressure (EIOP) with single topical agent for intervention; no visual field deficit imiting instrumental ADL Definition: A disorder characterized by an increase in pressure in the eyeball due to obstruction of the aqueous humor outflow. Keratitis Symptomatic: medical intervention indicated (e.g., topical agents); limiting instrumental ADL Definition: A disorder characterized by inflammation to the cornea of the eye. Night blindness Symptomatic but not limiting Limiting instrumental ADL Limiting self care ADL Limiting self care ADL Limiting self care ADL	Definition: A disorder characte	erized by impaired eyelid function	on.	T	I	Г
Symptomatic but not limiting ADL	Flashing lights		Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by an individual seeing spots before their eyes. The spots are shadows of opaque cell fragments in the vitreous humor or lens. Elevated intraocular pressure (EIOP) with single topical agent for intervention; no visual field deficit willing instrumental ADL Definition: A disorder characterized by an increase in pressure in the eyeball due to obstruction of the aqueous humor outflow. Keratitis - Symptomatic; medical intervention indicated (e.g., topical agents); limiting agents in the eyeball due to obstruction of the aqueous humor outflow. Definition: A disorder characterized by inflammation to the cornea of the eye. Night blindness Symptomatic but not limiting Limiting instrumental ADL Limiting self care ADL Limiting self care ADL Blindness (20/200 or worse) -	Definition: A disorder characte	erized by a sudden or brief burs	t of light.	I	T	Ι
Elevated intraocular pressure (EIOP) with single topical agent for intervention; no visual field deficit imiting instrumental ADL Definition: A disorder characterized by an increase in pressure in the eyeball due to obstruction of the aqueous humor outflow. Symptomatic; medical intervention indicated (e.g., topical agents); limiting agent of the aqueous humor outflow. Symptomatic; medical intervention indicated (e.g., topical agents); limiting agent of the aqueous humor outflow. Definition: A disorder characterized by an increase in pressure in the eyeball due to obstruction of the aqueous humor outflow. Symptomatic; medical intervention indicated (e.g., topical agents); limiting 20/40 but better than 20/200); limiting self care ADL Definition: A disorder characterized by inflammation to the cornea of the eye. Night blindness Symptomatic but not limiting Limiting instrumental ADL EIOP causing marked visual field deficits (e.g., involving both superior and inferior visual field deficits (e.g., involving both superior and inferior visual field deficits (e.g., involving both superior and inferior visual field deficits (e.g., involving both superior and inferior visual field deficits (e.g., involving both superior and inferior visual field deficits (e.g., involving both superior and inferior visual field deficits (e.g., involving both superior and inferior visual field deficits (e.g., involving both superior and inferior visual field deficits (e.g., involving both superior and inferior visual field deficits (e.g., involving both superior and inferior visual field deficits (e.g., involving both superior and inferior visual field deficits (e.g., involving both superior and inferior visual field deficits (e.g., involving both superior and inferior visual field deficits (e.g., involving both superior and inferior visual field deficits (e.g., involving both superior and inferior visual field deficits (e.g., involving both superior and inferior visual field deficits (e.g., involving both superior and inferior vi	Floaters		Limiting instrumental ADL	Limiting self care ADL	-	-
pressure (EIOP) with single topical agent for intervention; no visual field deficit witing instrumental ADL initing self care ADL Definition: A disorder characterized by an increase in pressure in the eyeball due to obstruction of the aqueous humor outflow. Symptomatic; medical intervention indicated (e.g., topical agents); limiting 20/200); limiting self care ADL Definition: A disorder characterized by inflammation to the cornea of the eye. Night blindness Symptomatic but not limiting Limiting instrumental ADL Limiting self care ADL Limiting self care ADL Limiting self care ADL Limiting self care ADL Blindness (20/200 or worse) -	Definition: A disorder characte	erized by an individual seeing s I	pots before their eyes. The spo	ots are shadows of opaque cell	fragments in the vitreous hume	or or lens.
Symptomatic; medical intervention indicated (e.g., topical agents); limiting instrumental ADL Limiting self care ADL Decline in vision (worse than 20/40 but better than 20/200) Perforation or blindness (20/200 or worse) in the affected eye Perforation or blindness (20/200 or worse) in the affected eye Perforation or blindness (20/200 or worse) in the affected eye Perforation or blindness (20/200 or worse) P	Glaucoma	pressure (EIOP) with single topical agent for intervention;	field deficits; multiple topical or oral agents indicated;	field deficits (e.g., involving both superior and inferior visual fields); operative intervention indicated;	,	-
intervention indicated (e.g., topical agents); limiting instrumental ADL	Definition: A disorder characte	erized by an increase in pressu	re in the eyeball due to obstruc	ction of the aqueous humor out	flow.	
Night blindness Symptomatic but not limiting Limiting instrumental ADL Limiting self care ADL Blindness (20/200 or worse) -		-	intervention indicated (e.g., topical agents); limiting instrumental ADL	20/40 but better than 20/200); limiting self care	(20/200 or worse) in the	-
		1	·	1		
	Night blindness		Limiting instrumental ADL	Limiting self care ADL	, ,	-

		Eye dis	sorders		
			Grade		
Adverse Event	1	2	3	4	5
Optic nerve disorder	Asymptomatic; clinical or diagnostic observations only	Limiting vision of the affected eye (20/40 or better)	eye (worse than 20/40 but better than 20/200)	Blindness (20/200 or worse) in the affected eye	-
	erized by involvement of the op	·	i		I
Papilledema	Asymptomatic; no visual field defects	vision; visual field defect present sparing the central 20 degrees	Marked visual field defect (worse than 20/40 but better than 20/200)	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder charact	erized by swelling around the o	ptic disc.	I		I
Photophobia	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder charact	erized by fear and avoidance of	f light.	1	1	
Retinal detachment	Asymptomatic	Exudative and visual acuity 20/40 or better	Rhegmatogenous or exudative detachment; operative intervention indicated; decline in vision (worse than 20/40 but better than 20/200)	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder charact	erized by the separation of the	inner retina layers from the und	derlying pigment epithelium.		
Retinal tear	-	Laser therapy or pneumopexy indicated	Vitroretinal surgical repair indicated	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder charact	erized by a small laceration of t	he retina, this occurs when the	vitreous separates from the re	tina. Symptoms include flashes	and floaters.
Retinal vascular disorder	-	Topical medication indicated	Intravitreal medication; operative intervention indicated	-	-
Definition: A disorder charact	erized by pathological retinal bl	ood vessels that adversely affe	cts vision.		
Retinopathy	Asymptomatic; clinical or diagnostic observations only	Symptomatic with moderate decrease in visual acuity (20/40 or better); limiting instrumental ADL	Symptomatic with marked decrease in visual acuity (worse than 20/40); disabling; limiting self care ADL	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder involvin	g the retina.				
Scleral disorder	Asymptomatic; clinical or diagnostic observations only	Symptomatic, limiting instrumental ADL; moderate decrease in visual acuity (20/40 or better)	Symptomatic, limiting self care ADL; marked decrease in visual acuity (worse than 20/40)	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder charact	erized by involvement of the sc	lera of the eye.	T		T
Uveitis	Asymptomatic; clinical or diagnostic observations only	•	Posterior or pan-uveitis	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder charact	erized by inflammation to the uv	vea of the eye.	1	T	1
Vitreous hemorrhage	Asymptomatic or mild symptoms; clinical or diagnostic observations only	Symptomatic; limiting instrumental ADL	Limiting self care ADL; vitrectomy indicated	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder charact	erized by blood extravasation in	nto the vitreous humor.	T	Γ	T
Watering eyes	Intervention not indicated	Intervention indicated	Operative intervention indicated	-	-
Definition: A disorder of excess	ssive tearing in the eyes; it can	be caused by overproduction of	of tears or impaired drainage of	the tear duct.	
Eye disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately sight- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye	-

		Gastrointestinal dis	orders		
			Grade		
Adverse Event	1	2	3	4	5
Abdominal distension Definition: A disorder characteriz	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe discomfort; limiting self care ADL	-	-
		NA-d	0		
Abdominal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by a sensation of marked disco	omfort in the abdominal region.	T		1
Anal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by an abnormal communication	between the opening in the anal	canal to the perianal skin.	Ī	
Anal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by bleeding from the anal region		<u> </u>		1
Anal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by inflammation of the mucous	membrane of the anus.			
Anal necrosis	-	-	TPN or hospitalization indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
	ed by a necrotic process occurring		Ī		1
Anal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by a sensation of marked disco	omfort in the anal region.	T	T .	
Anal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Symptomatic and severely altered GI function; non- emergent operative intervention indicated; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteriz	ed by a narrowing of the lumen of	the anal canal.			
Anal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteriz	ed by a circumscribed, inflammato	ory and necrotic erosive lesion on t	he mucosal surface of the anal ca	nal.	
Ascites	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteriz	ed by accumulation of serous or h	emorrhagic fluid in the peritoneal	cavity.		
Bloating	No change in bowel function or oral intake	Symptomatic, decreased oral intake; change in bowel function	-	-	-
Definition: A disorder characteriz	ed by subject-reported feeling of u	incomfortable fullness of the abdor	men.		
Cecal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by bleeding from the cecum.				
Cheilitis	Asymptomatic; clinical or diagnostic observations only;	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; intervention indicated	-	-
	intervention not indicated				1

		Gastrointestinal dis	Grade		
Adverse Event	1	2	3	4	
Colitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder character	ized by inflammation of the colon.	1	1	İ	г
Colonic fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; bowel rest, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder character	ized by an abnormal communication	between the large intestine and a	another organ or anatomic site.	 	
Colonic hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder character	ized by bleeding from the colon.	Т	T	Г	
Colonic obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Hospitalization indicated; elective operative intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
	ized by blockage of the normal flow			Life in	Б "
Colonic perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	ized by a rupture in the colonic wall.				1
Colonic stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder character	ized by a narrowing of the lumen of	the colon.	,	•	•
Colonic ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder character	ized by a circumscribed, inflammato	ry and necrotic erosive lesion on t	the mucosal surface of the colon.		
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL	Obstipation with manual evacuation indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder character	ized by irregular and infrequent or d	ifficult evacuation of the bowels.			
Dental caries	One or more dental caries, not involving the root	Dental caries involving the root	Dental caries resulting in pulpitis or periapical abscess or resulting in tooth loss	-	-
Definition: A disorder character	ized by the decay of a tooth, in whice	h it becomes softened, discolored	and/or porous.		
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder character	ized by frequent and watery bowel r	novements.			
Dry mouth	Symptomatic (e.g., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva <0.1 ml/min	-	-

Gastrointestinal disorders Grade							
		_	Grade				
Adverse Event	1	2	3	4	5		
Duodenal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characte	erized by an abnormal communication	n between the duodenum and and	other organ or anatomic site.				
Duodenal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characte	erized by bleeding from the duodenur	n.	T	1			
Duodenal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Hospitalization or elective operative intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder characte	erized by blockage of the normal flow	of stomach contents through the	duodenum.				
Duodenal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder characte	erized by a rupture in the duodenal w	all.	1	1			
Duodenal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder characte	erized by a narrowing of the lumen of	the duodenum.					
Duodenal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder characte	erized by a circumscribed, inflammato	ory and necrotic erosive lesion on	the mucosal surface of the duoder	nal wall.			
Dyspepsia	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; surgical intervention indicated	-	-		
Definition: A disorder characte heartburn, nausea and vomiti	erized by an uncomfortable, often pai	nful feeling in the stomach, resulti	ing from impaired digestion. Sympt	oms include burning stomach, blo	ating,		
Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing	Severely altered eating/swallowing; tube feeding or TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characte	erized by difficulty in swallowing.	ı	1	1	'		
Enterocolitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe or persistent abdominal pain; fever; ileus; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characte	erized by inflammation of the small ar	nd large intestines.	_				
Enterovesical fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; noninvasive intervention indicated	Severe, medically significant; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characte	erized by an abnormal communication	between the urinary bladder and	d the intestine.				
Esophageal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characte	erized by an abnormal communication	n between the esophagus and an	other organ or anatomic site.	•			
Esophageal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor	Transfusion, radiologic, endoscopic, or elective	Life-threatening consequences; urgent intervention indicated	Death		

Gastrointestinal disorders							
			Grade		I		
Adverse Event	1	2	3	4	5		
Esophageal necrosis	-	-	Inability to aliment adequately by GI tract; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder character	rized by a necrotic process occurring	g in the esophageal wall.					
Esophageal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder character	rized by blockage of the normal flow	of the contents in the esophagus.	T	T			
Esophageal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-		
Definition: A disorder character	rized by a sensation of marked disco	omfort in the esophageal region.					
Esophageal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
	rized by a rupture in the wall of the e			T .			
Esophageal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder character	rized by a narrowing of the lumen of	the esophagus.					
Esophageal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder character	rized by a circumscribed, inflammato	ory and necrotic erosive lesion on	the mucosal surface of the esopha	ngeal wall.			
Esophageal varices nemorrhage	-	Self-limited; intervention not indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder character	rized by bleeding from esophageal v	rarices.					
Esophagitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered eating/swallowing; oral supplements indicated	Severely altered eating/swallowing; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder character	rized by inflammation of the esopha	geal wall.					
Fecal incontinence	Occasional use of pads required	Daily use of pads required	Severe symptoms; elective operative intervention indicated	-	-		
Definition: A disorder character	rized by inability to control the escap	pe of stool from the rectum.	T	T			
Flatulence	Mild symptoms; intervention not indicated	Moderate; persistent; psychosocial sequelae	-	-	-		
Definition: A disorder character	rized by a state of excessive gas in t	the alimentary canal.	1	T			
Gastric fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; bowel rest; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
	rized by an abnormal communication						
Sastric hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder character	rized by bleeding from the gastric wa	all.					
Gastric necrosis	-	-	Inability to aliment adequately by GI tract; radiologic, endoscopic, or operative	Life-threatening consequences; urgent operative intervention indicated	Death		

Gastrointestinal disorders								
			Grade					
Adverse Event	1	2	3	4	5			
Gastric perforation Definition: A disorder characte	rized by a rupture in the stomach wa	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
			Caverely altered Cl functions	Life threatening concessions	Dooth			
Gastric stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characte	rized by a narrowing of the lumen of	the stomach.						
Gastric ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death			
	rized by a circumscribed, inflammato	ľ			1			
Gastritis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated	Severely altered eating or gastric function; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characte	rized by inflammation of the stomach	n.	1					
Gastroesophageal reflux disease	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; surgical intervention indicated	-	-			
	rized by reflux of the gastric and/or d y result in injury to the esophageal m			nd usually caused by incompetend	e of the lo			
Gastrointestinal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characte	rized by an abnormal communication	between any part of the gastroin	testinal system and another organ	or anatomic site.				
Gastrointestinal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characte	rized by a sensation of marked disco	omfort in the gastrointestinal region	1.					
Gastroparesis	Mild nausea, early satiety and bloating, able to maintain caloric intake on regular diet	Moderate symptoms; able to maintain nutrition with dietary and lifestyle modifications; may need pharmacologic intervention	Weight loss; refractory to medical intervention; unable to maintain nutrition orally	-	-			
Definition: A disorder characte	rized by an incomplete paralysis of the	he muscles of the stomach wall re	sulting in delayed emptying of the	gastric contents into the small inte	estine.			
Gingival pain	Mild pain	Moderate pain interfering with oral intake	Severe pain; inability to aliment orally	-	-			
Definition: A disorder characte	rized by a sensation of marked disco	omfort in the gingival region.	T	1				
Hemorrhoidal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characte	rized by bleeding from the hemorrho	ids.						
Hemorrhoids	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; banding or medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	-	-			
Definition: A disorder characte	rized by the presence of dilated vein	s in the rectum and surrounding a	rea.					
lleal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characte	rized by an abnormal communication	between the ileum and another o	organ or anatomic site.					
	Milds intersentian not indicated	Moderate symptoms; medical	Transfusion, radiologic,	Life-threatening consequences;	Death			
lleal hemorrhage	Mild; intervention not indicated	intervention or minor cauterization indicated	endoscopic, or elective operative intervention indicated	urgent intervention indicated				

		Gastrointestinal dis			
			Grade		
Adverse Event	1	2	3	4	5
leal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteriz	zed by blockage of the normal flow	of the intestinal contents in the il-	eum.	1	
lleal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteriz	zed by a rupture in the ileal wall.				
lleal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterize	zed by a narrowing of the lumen of	the ileum.	T	T	
lleal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterize	zed by a circumscribed, inflammate	ory and necrotic erosive lesion on	the mucosal surface of the ileum.	T	
lleus	- zed by failure of the ileum to transp	Symptomatic; altered GI function; bowel rest indicated	Severely altered GI function; TPN indicated	Life-threatening consequences; urgent intervention indicated	Death
Intra-abdominal hemorrhage	zed by failure of the fleuth to trainsp	Medical intervention or minor	Transfusion, radiologic,	Life-threatening consequences;	Death
mila-abuomiliai nemormaye		cauterization indicated	endoscopic, or elective operative intervention indicated	urgent intervention indicated	Death
Definition: A disorder characteriz	zed by bleeding in the abdominal c	avity.	_		
Jejunal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteria	्। zed by an abnormal communicatio।	n between the jejunum and anoth	er organ or anatomic site.	ı	'
Jejunal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	zed by bleeding from the jejunal wa	all.		•	
Jejunal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteriz	zed by blockage of the normal flow	of the intestinal contents in the je	ejunum.		
Jejunal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteria	' zed by a rupture in the jejunal wall.	'	•	'	'
Jejunal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteriz	zed by a narrowing of the lumen of	the jejunum.	<u> </u>	·	
Jejunal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteriz	zed by a circumscribed, inflammato	ory and necrotic erosive lesion on	the mucosal surface of the jejunun	1.	
_ip pain	Mild pain	Moderate pain; limiting	Severe pain; limiting self care	-	-

Gastrointestinal disorders								
			Grade					
Adverse Event	1	2	3	4	5			
ower gastrointestinal	Mild; intervention not indicated	Moderate symptoms; medical	Transfusion, radiologic,	Life-threatening consequences;	Death			
nemorrhage		intervention or minor	endoscopic, or elective	urgent intervention indicated				
5.5 W. A.P. I. I. I.		cauterization indicated	operative intervention indicated					
	erized by bleeding from the lower gas				I			
Malabsorption	-	Altered diet; oral intervention indicated	Inability to aliment adequately; TPN indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characte	erized by inadequate absorption of nu	utrients in the small intestine. Sym	ptoms include abdominal marked	discomfort, bloating and diarrhea.				
Mucositis oral	Asymptomatic or mild	Moderate pain; not interfering	Severe pain; interfering with oral	Life-threatening consequences;	Death			
	symptoms; intervention not	with oral intake; modified diet	intake	urgent intervention indicated				
	indicated	indicated	I		I			
Definition: A disorder characte	erized by inflammation of the oral mu	cosal.	1	T	1			
Nausea	Loss of appetite without	Oral intake decreased without	Inadequate oral caloric or fluid	-	-			
	alteration in eating habits	significant weight loss,	intake; tube feeding, TPN, or					
D-6:iti		dehydration or malnutrition	hospitalization indicated		l			
	erized by a queasy sensation and/or t		11	1 15- 41	D"			
Obstruction gastric	Asymptomatic; clinical or diagnostic observations only;	Symptomatic; altered GI function; limiting instrumental	Hospitalization indicated; elective operative intervention	Life-threatening consequences; urgent operative intervention	Death			
	intervention not indicated	ADL	indicated; limiting self care ADL;	indicated				
			disabling					
Definition: A disorder characte	rized by blockage of the normal flow	of the contents in the stomach.	•	•	•			
Oral cavity fistula	Asymptomatic; clinical or	Symptomatic; altered GI	Severely altered GI function;	Life-threatening consequences;	Death			
•	diagnostic observations only;	function	TPN or hospitalization indicated;	urgent intervention indicated				
	intervention not indicated		elective operative intervention					
			indicated					
Definition: A disorder characte	erized by an abnormal communication	n between the oral cavity and ano	ther organ or anatomic site.					
Oral dysesthesia	Mild discomfort; not interfering	Moderate pain; interfering with	Disabling pain; tube feeding or	-	-			
	with oral intake	oral intake	TPN indicated					
Definition: A disorder characte	erized by a burning or tingling sensati	ion on the lips, tongue or entire mo	outh.	T				
Oral hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical	Transfusion, radiologic,	Life-threatening consequences;	Death			
		intervention or minor	endoscopic, or elective	urgent intervention indicated				
		cauterization indicated	operative intervention indicated		l			
Definition: A disorder characte								
	erized by bleeding from the mouth.							
Oral pain	Mild pain	Moderate pain; limiting	Severe pain; limiting self care	-	-			
	Mild pain	instrumental ADL	ADL	-	-			
	Mild pain	instrumental ADL	ADL .	-	-			
	Mild pain Prized by a sensation of marked disconsisted Asymptomatic; clinical or	instrumental ADL omfort in the mouth, tongue or lips Symptomatic; altered GI	ADL Severely altered GI function;	Life-threatening consequences;	- Death			
Definition: A disorder characte	Mild pain Prized by a sensation of marked disconsisted asymptomatic; clinical or diagnostic observations only;	instrumental ADL	Severely altered GI function; tube feeding or hospitalization	urgent operative intervention	- Death			
Definition: A disorder characte	Mild pain Prized by a sensation of marked disconsisted Asymptomatic; clinical or	instrumental ADL omfort in the mouth, tongue or lips Symptomatic; altered GI	ADL Severely altered GI function;		- Death			
Definition: A disorder characte Pancreatic duct stenosis	Mild pain erized by a sensation of marked disconsisted and a sensation and a sens	instrumental ADL pmfort in the mouth, tongue or lips Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative	urgent operative intervention	- Death			
Definition: A disorder characte Pancreatic duct stenosis Definition: A disorder characte	Mild pain Perized by a sensation of marked disconsisted and the sense of the sense	instrumental ADL pmfort in the mouth, tongue or lips Symptomatic; altered GI function the pancreatic duct.	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	urgent operative intervention indicated				
Definition: A disorder characte Pancreatic duct stenosis Definition: A disorder characte	Mild pain erized by a sensation of marked disconsisted and a sensation and a sens	instrumental ADL pmfort in the mouth, tongue or lips Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative	urgent operative intervention	Death Death			
Definition: A disorder characte Pancreatic duct stenosis Definition: A disorder characte	Mild pain Perized by a sensation of marked disconsisted and a sensation of marked disconsisted and a sensation of marked disconsisted and a sensation and a s	instrumental ADL pmfort in the mouth, tongue or lips Symptomatic; altered GI function the pancreatic duct. Symptomatic; altered GI	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated Severely altered GI function;	urgent operative intervention indicated Life-threatening consequences;				
Definition: A disorder characte Pancreatic duct stenosis Definition: A disorder characte	Mild pain Perized by a sensation of marked disconsisted and a sensation of marked disconsisted and a sensation of marked disconsisted and a sensation and a s	instrumental ADL pmfort in the mouth, tongue or lips Symptomatic; altered GI function the pancreatic duct. Symptomatic; altered GI	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated Severely altered GI function; tube feeding or TPN or hospitalization indicated; elective operative intervention	urgent operative intervention indicated Life-threatening consequences; urgent operative intervention				
Definition: A disorder characte Pancreatic duct stenosis Definition: A disorder characte	Mild pain Perized by a sensation of marked disconsisted and a sensation of marked disconsisted and a sensation of marked disconsisted and a sensation and a s	instrumental ADL pmfort in the mouth, tongue or lips Symptomatic; altered GI function the pancreatic duct. Symptomatic; altered GI	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated Severely altered GI function; tube feeding or TPN or hospitalization indicated;	urgent operative intervention indicated Life-threatening consequences; urgent operative intervention				
Definition: A disorder characte Pancreatic duct stenosis Definition: A disorder characte Pancreatic fistula	Mild pain Perized by a sensation of marked disconsisted and a sensation of marked disconsisted and a sensation of marked disconsisted and a sensation and a s	instrumental ADL pmfort in the mouth, tongue or lips Symptomatic; altered GI function the pancreatic duct. Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated Severely altered GI function; tube feeding or TPN or hospitalization indicated; elective operative intervention indicated	urgent operative intervention indicated Life-threatening consequences; urgent operative intervention				
Definition: A disorder character Pancreatic duct stenosis Definition: A disorder character Pancreatic fistula Definition: A disorder character	Mild pain Asymptomatic; clinical or diagnostic observations only; intervention not indicated Asymptomatic; clinical or diagnostic observations only; intervention not indicated	instrumental ADL pmfort in the mouth, tongue or lips Symptomatic; altered GI function the pancreatic duct. Symptomatic; altered GI function between the pancreas and anoth Moderate symptoms; medical	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated Severely altered GI function; tube feeding or TPN or hospitalization indicated; elective operative intervention indicated ner organ or anatomic site. Transfusion, radiologic,	urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences;				
Definition: A disorder character Pancreatic duct stenosis Definition: A disorder character Pancreatic fistula Definition: A disorder character	Mild pain Perized by a sensation of marked discording discording and the sense of	instrumental ADL pmfort in the mouth, tongue or lips Symptomatic; altered GI function the pancreatic duct. Symptomatic; altered GI function between the pancreas and anoth Moderate symptoms; medical intervention or minor	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated Severely altered GI function; tube feeding or TPN or hospitalization indicated; elective operative intervention indicated ner organ or anatomic site. Transfusion, radiologic, endoscopic, or elective	urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder character Pancreatic duct stenosis Definition: A disorder character Pancreatic fistula Definition: A disorder character Pancreatic hemorrhage	Mild pain Asymptomatic; clinical or diagnostic observations only; intervention not indicated Asymptomatic; clinical or diagnostic observations only; intervention not indicated Asymptomatic; clinical or diagnostic observations only; intervention not indicated Asymptomatic; clinical or diagnostic observations only; intervention not indicated Mild; intervention not indicated	instrumental ADL omfort in the mouth, tongue or lips Symptomatic; altered GI function the pancreatic duct. Symptomatic; altered GI function between the pancreas and anott Moderate symptoms; medical intervention or minor cauterization indicated	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated Severely altered GI function; tube feeding or TPN or hospitalization indicated; elective operative intervention indicated ner organ or anatomic site. Transfusion, radiologic,	urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences;	Death			
Definition: A disorder character Pancreatic duct stenosis Definition: A disorder character Pancreatic fistula Definition: A disorder character Pancreatic fistula	Mild pain Perized by a sensation of marked discording discording and the sense of	instrumental ADL omfort in the mouth, tongue or lips Symptomatic; altered GI function the pancreatic duct. Symptomatic; altered GI function between the pancreas and anott Moderate symptoms; medical intervention or minor cauterization indicated	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated Severely altered GI function; tube feeding or TPN or hospitalization indicated; elective operative intervention indicated ner organ or anatomic site. Transfusion, radiologic, endoscopic, or elective operative intervention indicated	urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences;	Death			
Definition: A disorder character Pancreatic duct stenosis Definition: A disorder character Pancreatic fistula Definition: A disorder character Pancreatic fistula	Mild pain Asymptomatic; clinical or diagnostic observations only; intervention not indicated Asymptomatic; clinical or diagnostic observations only; intervention not indicated Asymptomatic; clinical or diagnostic observations only; intervention not indicated Asymptomatic; clinical or diagnostic observations only; intervention not indicated Mild; intervention not indicated	instrumental ADL omfort in the mouth, tongue or lips Symptomatic; altered GI function the pancreatic duct. Symptomatic; altered GI function between the pancreas and anott Moderate symptoms; medical intervention or minor cauterization indicated	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated Severely altered GI function; tube feeding or TPN or hospitalization indicated; elective operative intervention indicated ner organ or anatomic site. Transfusion, radiologic, endoscopic, or elective operative intervention indicated	urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder character Pancreatic duct stenosis Definition: A disorder character Pancreatic fistula Definition: A disorder character Pancreatic hemorrhage	Mild pain Asymptomatic; clinical or diagnostic observations only; intervention not indicated Asymptomatic; clinical or diagnostic observations only; intervention not indicated Asymptomatic; clinical or diagnostic observations only; intervention not indicated Asymptomatic; clinical or diagnostic observations only; intervention not indicated Mild; intervention not indicated	instrumental ADL omfort in the mouth, tongue or lips Symptomatic; altered GI function the pancreatic duct. Symptomatic; altered GI function between the pancreas and anott Moderate symptoms; medical intervention or minor cauterization indicated	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated Severely altered GI function; tube feeding or TPN or hospitalization indicated; elective operative intervention indicated ner organ or anatomic site. Transfusion, radiologic, endoscopic, or elective operative intervention indicated	urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent intervention indicated Life-threatening consequences; urgent operative intervention	Death			
Definition: A disorder character Pancreatic duct stenosis Definition: A disorder character Pancreatic fistula Definition: A disorder character Pancreatic hemorrhage Definition: A disorder character Pancreatic hemorrhage	Mild pain Asymptomatic; clinical or diagnostic observations only; intervention not indicated Asymptomatic; clinical or diagnostic observations only; intervention not indicated Asymptomatic; clinical or diagnostic observations only; intervention not indicated Asymptomatic; clinical or diagnostic observations only; intervention not indicated Mild; intervention not indicated	instrumental ADL omfort in the mouth, tongue or lips Symptomatic; altered GI function the pancreatic duct. Symptomatic; altered GI function n between the pancreas and anote Moderate symptoms; medical intervention or minor cauterization indicated	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated Severely altered GI function; tube feeding or TPN or hospitalization indicated; elective operative intervention indicated ner organ or anatomic site. Transfusion, radiologic, endoscopic, or elective operative intervention indicated	urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder character Pancreatic duct stenosis Definition: A disorder character Pancreatic fistula Definition: A disorder character Pancreatic hemorrhage Definition: A disorder character Pancreatic necrosis	Mild pain Asymptomatic; clinical or diagnostic observations only; intervention not indicated Asymptomatic; clinical or diagnostic observations only; intervention not indicated Asymptomatic; clinical or diagnostic observations only; intervention not indicated Asymptomatic; clinical or diagnostic observations only; intervention not indicated Mild; intervention not indicated	instrumental ADL omfort in the mouth, tongue or lips Symptomatic; altered GI function the pancreatic duct. Symptomatic; altered GI function n between the pancreas and anott Moderate symptoms; medical intervention or minor cauterization indicated -	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated Severely altered GI function; tube feeding or TPN or hospitalization indicated; elective operative intervention indicated ner organ or anatomic site. Transfusion, radiologic, endoscopic, or elective operative intervention indicated Tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent intervention indicated Life-threatening consequences; urgent operative intervention indicated	Death Death			
Definition: A disorder character Pancreatic duct stenosis Definition: A disorder character Pancreatic fistula Definition: A disorder character Pancreatic hemorrhage Definition: A disorder character Pancreatic hemorrhage	Mild pain Asymptomatic; clinical or diagnostic observations only; intervention not indicated Asymptomatic; clinical or diagnostic observations only; intervention not indicated Asymptomatic; clinical or diagnostic observations only; intervention not indicated Asymptomatic; clinical or diagnostic observations only; intervention not indicated Mild; intervention not indicated	instrumental ADL omfort in the mouth, tongue or lips Symptomatic; altered GI function the pancreatic duct. Symptomatic; altered GI function n between the pancreas and anote Moderate symptoms; medical intervention or minor cauterization indicated	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated Severely altered GI function; tube feeding or TPN or hospitalization indicated; elective operative intervention indicated ner organ or anatomic site. Transfusion, radiologic, endoscopic, or elective operative intervention indicated	urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent intervention indicated Life-threatening consequences; urgent operative intervention	Death			

Gastrointestinal disorders								
			Grade		I			
Adverse Event	1	2	3	4	5			
Definition: A disorder characte	rized by inflammation of the pancrea	S.		<u> </u>	1			
Periodontal disease	Gingival recession or gingivitis; limited bleeding on probing; mild local bone loss	Moderate gingival recession or gingivitis; multiple sites of bleeding on probing; moderate bone loss	Spontaneous bleeding; severe bone loss with or without tooth loss; osteonecrosis of maxilla or mandible	-	-			
	ngival tissue around the teeth.	<u> </u>		1	1			
Peritoneal necrosis	-	-	Tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characte	rized by a necrotic process occurring	in the peritoneum.		T				
Proctitis	Rectal discomfort, intervention not indicated	Symptoms (e.g., rectal discomfort, passing blood or mucus); medical intervention indicated; limiting instrumental ADL	Severe symptoms; fecal urgency or stool incontinence; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characte	rized by inflammation of the rectum.							
Rectal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characte	rized by an abnormal communication	between the rectum and another	r organ or anatomic site.					
Rectal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characte	rized by bleeding from the rectal wall	and discharged from the anus.						
Rectal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characte	rized by inflammation of the mucous	membrane of the rectum.	_					
Rectal necrosis	-	-	Tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characte	rized by a necrotic process occurring	in the rectal wall.		T				
Rectal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characte	rized by blockage of the normal flow	of the intestinal contents in the re		Г				
Rectal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
	rized by a sensation of marked disco		T_	I	_			
Rectal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characte	rized by a rupture in the rectal wall.							
Rectal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characte	rized by a narrowing of the lumen of	the rectum.						
Rectal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function (e.g. altered dietary habits, vomiting, diarrhea)	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death			

		Gastrointestinal dis	orders		
		T	Grade		
Adverse Event	1	2	3	4	5
Retroperitoneal hemorrhage	- zed by bleeding from the retroperite	Self-limited; intervention indicated	Transfusion, medical, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
			A 4 15	1 15- 41	D 41-
Salivary duct inflammation	Slightly thickened saliva; slightly altered taste (e.g., metallic)	Thick, ropy, sticky saliva; markedly altered taste; alteration in diet indicated; secretion-induced symptoms; limiting instrumental ADL	Acute salivary gland necrosis; severe secretion-induced symptoms (e.g., thick saliva/oral secretions or gagging); tube feeding or TPN indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	zed by inflammation of the salivary	duct.			
Salivary gland fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; tube feeding indicated	Severely altered GI function; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteriz	zed by an abnormal communication	n between a salivary gland and an	other organ or anatomic site.		
Small intestinal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe pain; interfering with oral intake; tube feeding, TPN or hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by inflammation of the mucous	membrane of the small intestine.			
Small intestinal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteriz	ed by blockage of the normal flow	of the intestinal contents.			
Small intestinal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteriz	red by a rupture in the small intesti	ne wall.			
Small intestinal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Symptomatic and severely altered GI function; tube feeding, TPN or hospitalization indicated; non-emergent operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteriz	ed by a narrowing of the lumen of	the small intestine.			
Small intestine ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteriz	red by a circumscribed, inflammato	ory and necrotic erosive lesion on t	the mucosal surface of the small in	testine.	
Stomach pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterize	red by a sensation of marked disco	omfort in the stomach.	1		
Tooth development disorder	Asymptomatic; hypoplasia of tooth or enamel	Impairment correctable with oral surgery	Maldevelopment with impairment not surgically correctable; disabling	-	-
Definition: A disorder characterize	red by a pathological process of th	e teeth occurring during tooth deve	elopment.		
Tooth discoloration	Surface stains	-	-	-	-
Definition: A disorder characterize	red by a change in tooth hue or tin	t.	1		
Toothache	Mild pain	Moderate pain; limiting	Severe pain; limiting self care	_	l -

		Gastrointestinal dis	orders			
Grade						
Adverse Event	1	2	3	4	5	
Typhlitis	-	-	Symptomatic (e.g., abdominal pain, fever, change in bowel habits with ileus); peritoneal signs	Life-threatening consequences; urgent operative intervention indicated	Death	
Definition: A disorder characteriz	ed by inflammation of the cecum.		,	•		
Upper gastrointestinal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characteriz	ed by bleeding from the upper gas	trointestinal tract (oral cavity, pha	rynx, esophagus, and stomach).			
Vomiting	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	>=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characteriz	ed by the reflexive act of ejecting t	he contents of the stomach throuç	gh the mouth.	•		
Gastrointestinal disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	

			Grade		
Adverse Event	1	2	3	4	5
Chills	Mild sensation of cold; shivering; chattering of teeth	Moderate tremor of the entire body; narcotics indicated	Severe or prolonged, not responsive to narcotics	-	-
Definition: A disorder charac	sterized by a sensation of cold that ofte	1	1 '	I	
Death neonatal	-	-	-	-	Death
Definition: A disorder charac	terized by cessation of life occurring de	uring the first 28 days of life.			
Death NOS	-	-	-	-	Death
Definition: A cessation of life	that cannot be attributed to a CTCAE	term associated with Grade 5.			
Edema face	Localized facial edema	Moderate localized facial edema; limiting instrumental ADL	Severe swelling; limiting self care ADL	-	-
Definition: A disorder charac	eterized by swelling due to excessive flu	uid accumulation in facial tissues.	I	1	
Edema limbs	5 - 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection	>10 - 30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL	>30% inter-limb discrepancy in volume; gross deviation from normal anatomic contour; limiting self care ADL	-	-
Definition: A disorder charac	sterized by swelling due to excessive flu	uid accumulation in the upper or lo	wer extremities.		
Edema trunk	Swelling or obscuration of anatomic architecture on close inspection	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL	Gross deviation from normal anatomic contour; limiting self care ADL	-	-
Facial pain	terized by swelling due to excessive flu	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care	-	-
Definition: A disorder charac	ा sterized by a sensation of marked disco	1	I	I	ı
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL	-	-
Definition: A disorder charac	sterized by a state of generalized weak	ness with a pronounced inability to	summon sufficient energy to acc	omplish daily activities.	
Fever	38.0 - 39.0 degrees C (100.4 - 102.2 degrees F)	>39.0 - 40.0 degrees C (102.3 - 104.0 degrees F)	>40.0 degrees C (>104.0 degrees F) for <=24 hrs	>40.0 degrees C (>104.0 degrees F) for >24 hrs	Death
Definition: A disorder charac	terized by elevation of the body's temp	perature above the upper limit of no	ormal.	1	
Flu like symptoms	Mild flu-like symptoms present	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder charac cough.	sterized by a group of symptoms simila	r to those observed in patients with	n the flu. It includes fever, chills, b	ody aches, malaise, loss of appeti	te and dry
Gait disturbance	Mild change in gait (e.g., wide- based, limping or hobbling)	Moderate change in gait (e.g., wide-based, limping or hobbling); assistive device indicated; limiting instrumental ADL	Disabling; limiting self care ADL	-	-
	eterized by walking difficulties.	05 - 00 0 - 05	20 - 20	1-00 d C 00 4 1	D"
Hypothermia	-	35 - >32 degrees C; 95 - >89.6 degrees F	32 - >28 degrees C; 89.6 - >82.4 degrees F	<=28 degrees C; 82.4 degrees F; life-threatening consequences (e.g., coma, hypotension, pulmonary edema, acidemia, ventricular fibrillation)	Death

	Jeneral	disorders and administra		Grade							
Adverse Event	1	2	3	4	5						
Infusion related reaction	Mild transient reaction; infusion	Therapy or infusion interruption	Prolonged (e.g., not rapidly	Life-threatening consequences;	Death						
illiusion relateu reaction	interruption not indicated;	indicated but responds promptly	responsive to symptomatic	urgent intervention indicated	Dealii						
	intervention not indicated	to symptomatic treatment (e.g.,	medication and/or brief	argont intervention indicated							
	micromicri net maleatea	antihistamines, NSAIDS,	interruption of infusion);								
		narcotics, IV fluids); prophylactic	· · · · · · · · · · · · · · · · · · ·								
		medications indicated for <=24	following initial improvement;								
		hrs	hospitalization indicated for								
			clinical sequelae								
Definition: A disorder characteriz	red by adverse reaction to the infus	। sion of pharmacological or biologic	1	ı	'						
nfusion site extravasation	-	Erythema with associated	Ulceration or necrosis; severe	Life-threatening consequences;	Death						
		symptoms (e.g., edema, pain,	tissue damage; operative	urgent intervention indicated							
		induration, phlebitis)	intervention indicated								
Definition: A disorder characteriz	ed by leakage of a pharmacologic	, , , , ,	1	ı ssue. Signs and symptoms includ	। e induratio						
	sation and marked discomfort at the	•	ao.o o.co i.i.o a.i.o oai. oai.i.ai.i.g a.	oodo. Olgilo alla ojilipiolilo illolad	o maaram						
Injection site reaction	Tenderness with or without	Pain; lipodystrophy; edema;	Ulceration or necrosis; severe	Life-threatening consequences;	Death						
	associated symptoms (e.g.,	phlebitis	tissue damage; operative	urgent intervention indicated							
	warmth, erythema, itching)		intervention indicated								
Definition: A disorder characteriz	ed by an intense adverse reaction	(usually immunologic) developing	at the site of an injection.		•						
Irritability	Mild; easily consolable	Moderate; limiting instrumental	Severe abnormal or excessive	-	-						
ŕ		ADL; increased attention	response; limiting self care ADL;								
		indicated	inconsolable								
Definition: A disorder characteriz	red by an abnormal responsivenes	ı s to stimuli or physiological arousa	1	I ht_a drug_an emotional situation	ı or a medic						
condition.	sa by an abnormal responsivenes	o to difficill of physiological aroust	ar, may be in response to pain, mg	nt, a drug, an omotional oldation	or a moun						
Localized edema	Localized to dependent areas,	Moderate localized edema and	Severe localized edema and	-	-						
	no disability or functional	intervention indicated; limiting	intervention indicated; limiting								
	impairment	instrumental ADL	self care ADL								
Definition: A disorder characteriz	ed by swelling due to excessive flu	ı	1	ı	1						
Malaise	Uneasiness or lack of well being		_		I .						
Malaioo	Officed in control well being	being; limiting instrumental ADL									
Definition: A disorder characteriz	। ed by a feeling of general discomf		I feeling	ı	1						
Multi-organ failure	garby a recining or general alcooming		Shock with azotemia and acid-	Life-threatening consequences	Death						
Multi-organ fandre	-		base disturbances; significant	(e.g., vasopressor dependent	Death						
			coagulation abnormalities	and oliguric or anuric or							
			Coagulation apriormanties	ischemic colitis or lactic							
				acidosis)							
Definition: A disorder characteria	l red by progressive deterioration of	the lungs liver kidney and clottin	a machanisms	(doldoolo)	1						
Neck edema	Asymptomatic localized neck	Moderate neck edema; slight	Generalized neck edema (e.g.,	_	I_						
Neck edema	edema	obliteration of anatomic	difficulty in turning neck);	-	-						
	edellia	landmarks; limiting instrumental	limiting self care ADL								
		ADL	and ADE								
Definition: A disorder characteriz	। ed by swelling due to an accumula	ı		I	1						
Non-cardiac chest pain	Mild pain	Moderate pain; limiting	Severe pain; limiting self care	_							
Non-cardiac chest pain	Willia palif	instrumental ADL	ADL	-	-						
Definition: A disorder characterize	। ed by discomfort in the chest unre	ı	1	ı	I						
Pain	Mild pain	Moderate pain; limiting	Severe pain; limiting self care		Ι.						
MIT	wind pain	instrumental ADL	ADL								
Definition: A disorder characterize	l ed by the sensation of marked dis	ı	I	I	I						
Sudden death NOS	- uno obligation of marked dis	-	_	-	Death						
	- tion of life that cannot be attributed	I to a CTCAE term associated with	Grade 5	I	Deall						
•				Life threatening con	Do ati-						
General disorders and	Asymptomatic or mild	Moderate; minimal, local or	Severe or medically significant but not immediately life-	Life-threatening consequences;	Death						
administration site conditions -	symptoms; clinical or diagnostic	noninvasive intervention	1	urgent intervention indicated							
Other, specify	observations only; intervention	indicated; limiting age-	threatening; hospitalization or								
	not indicated	appropriate instrumental ADL									
			Incenitalization indicated:	1	i						
	not indicated	appropriate instrumental ADL	prolongation of existing hospitalization indicated;								

Hepatobiliary disorders							
	Grade						
Adverse Event	1	2	3	4	5		
Bile duct stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; IV fluids indicated <24 hrs	Severely altered GI function; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder characteri	zed by a narrowing of the lumen of	the bile duct.	1	I			
Biliary fistula	-	Symptomatic and intervention not indicated	Severely altered GI function; TPN indicated; endoscopic intervention indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder characteri	zed by an abnormal communication	n between the bile ducts and anoth	ner organ or anatomic site.	ı			
Cholecystitis	-	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder characteri	zed by inflammation involving the g	allbladder. It may be associated w	vith the presence of gallstones.				
Gallbladder fistula	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Symptomatic or severely altered GI function; TPN indicated; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder characteri	zed by an abnormal communication	n between the gallbladder and and	other organ or anatomic site.				
Gallbladder necrosis	-	-	-	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death		
Definition: A disorder characteri	zed by a necrotic process occurring	g in the gallbladder.	T	r			
Gallbladder obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; IV fluids indicated <24 hrs	Symptomatic and severely altered GI function; tube feeding, TPN or hospitalization indicated; non-emergent operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
	zed by blockage of the normal flow				1		
Gallbladder pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-		
Definition: A disorder characteri	zed by a sensation of marked disco	omfort in the gallbladder region.					
Gallbladder perforation	-	-	-	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteri	zed by a rupture in the gallbladder	wall.	Asterixis; mild encephalopathy; limiting self care ADL	Moderate to severe encephalopathy; coma; life-threatening consequences	Death		
	zed by the inability of the liver to me	etabolize chemicals in the body. L	aboratory test results reveal abnor	mal plasma levels of ammonia, bi	lirubin, lac		
dehydrogenase, and alkaline ph Hepatic hemorrhage	Mild; intervention not indicated	Symptomatic; medical	Transfusion indicated	Life-threatening consequences;	Death		
перацс петоппаде	wind, intervention not indicated	intervention indicated	Transiusion indicated	urgent intervention indicated	Death		
Definition: A disorder characteri	zed by bleeding from the liver.			T			
Hepatic necrosis	-	-	-	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death		
Definition: A disorder characteri	zed by a necrotic process occurring	g in the hepatic parenchyma.	T	Γ			
Hepatic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-		
Definition: A disorder characteri	zed by a sensation of marked disco	omfort in the liver region.					
Perforation bile duct	-	-	Radiologic, endoscopic or elective operative intervention	Life-threatening consequences; urgent operative intervention	Death		

	Hepatobiliary disorders									
		Grade								
Adverse Event	1	2	3	4	5					
Portal hypertension	-	Decreased portal vein flow	Reversal/retrograde portal vein flow; associated with varices and/or ascites	Life-threatening consequences; urgent intervention indicated	Death					
Definition: A disorder characterize	ed by an increase in blood pressui	re in the portal venous system.								
Portal vein thrombosis	-	Intervention not indicated	Medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death					
Definition: A disorder characterize	ed by the formation of a thrombus	(blood clot) in the portal vein.								
Hepatobiliary disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated;	Life-threatening consequences; urgent intervention indicated	Death					
			disabling; limiting self care ADL							

		Immune system dis	orders		
			Grade		
Adverse Event	1	2	3	4	5
Allergic reaction	Transient flushing or rash, drug fever <38 degrees C (<100.4 degrees F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
	ed by an adverse local or general	response from exposure to an alle			
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
	ed by an acute inflammatory react resents with breathing difficulty, dia				ypersensitivit
Autoimmune disorder	Asymptomatic; serologic or other evidence of autoimmune reaction, with normal organ function; intervention not indicated	Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism)	Autoimmune reactions involving major organ (e.g., colitis, anemia, myocarditis, kidney)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder resulting frontier	om loss of function or tissue destru	uction of an organ or multiple orga	ns, arising from humoral or cellula	r immune responses of the individ	ual to his owr
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilatory support indicated	Death
Definition: A disorder characteriz	ed by nausea, headache, tachyca	rdia, hypotension, rash, and short	ness of breath; it is caused by the	release of cytokines from the cells	
Serum sickness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate arthralgia; fever, rash, urticaria, antihistamines indicated	Severe arthralgia or arthritis; extensive rash; steroids or IV fluids indicated	Life-threatening consequences; pressor or ventilatory support indicated	Death
	ed by a delayed-type hypersensitive foreign antigen. Symptoms include				
Immune system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

		Infections and infes	tations			
			Grade		_	
Adverse Event	1	2	3	4	5	
Abdominal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characte	rized by an infectious process invol	ving the abdominal cavity.		1		
Anorectal infection	Localized; local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	
	rized by an infectious process invol	ving the anal area and the rectum.		Life threatening concession	Dooth	
Appendicitis	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	
	rized by acute inflammation to the v	rermiform appendix caused by a pa	athogenic agent.			
Appendicitis perforated	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	
	rized by acute inflammation to the viceal wall rupture causes the releas				ıne	
Arteritis infective	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characte	rized by an infectious process invol	ving an artery.		1		
Biliary tract infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characte	rized by an infectious process invol	ving the biliary tract.	•		•	
Bladder infection	-	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characte	rized by an infectious process invol	ving the bladder.				
Bone infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	
	rized by an infectious process invol					
Breast infection		Local infection with moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	Severe infection; axillary adenitis; IV antibacterial, antifungal, or antiviral intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	
Bronchial infection	rized by an infectious process invol	1	IV antibiotic antifungal or	Life threatening consequences:	Death	
BIOTICIIAI IIIIECUOTI		Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characte	rized by an infectious process invol	ving the bronchi.		1		
Catheter related infection	-	Localized; local intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characte	rized by an infectious process that	arises secondary to catheter use.				
Cecal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	

			Grade		
Adverse Event	1	2	3	4	5
Definition: A disorder characterize	ed by an infectious process involvi	ing the cecum.			
Cervicitis infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	ed by an infectious process involving			<u> </u>	
Conjunctivitis infective	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by an infectious process involvi	ing the conjunctiva. Clinical manife	estations include pink or red color	in the eyes.	
Corneal infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by an infectious process involvi	ing the cornea.			
Cranial nerve infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by an infectious process involve	ing a cranial nerve.			
Device related infection	-		IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	ed by an infectious process involvi				
Duodenal infection	-	Moderate symptoms; medical intervention indicated (e.g., oral antibiotics)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by an infectious process involvi	ing the duodenum.			
Encephalitis infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; severe changes in mental status; self-limited seizure activity; focal neurologic abnormalities	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by an infectious process involving	ing the brain tissue.	T	T	
Encephalomyelitis infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by an infectious process involvi	ing the brain and spinal cord tissu	es.		
Endocarditis infective	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by an infectious process involving	ing the endocardial layer of the he	art.	T	1
Endophthalmitis	l <u>-</u>	Local intervention indicated	Systemic intervention or	Blindness (20/200 or worse)	-

		Infections and infes			Grade							
Adverse Event	1	2	Grade 3	4	5							
	1											
Enterocolitis infectious		Passage of >3 unformed stools per 24 hrs or duration of illness >48 hrs; moderate abdominal pain	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated; profuse watery diarrhea with signs of hypovolemia; bloody diarrhea; fever; severe abdominal pain; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death							
Definition: Δ disorder character	I ized by an infectious process involv	ing the small and large intestines	Indicatod	I	I							
Esophageal infection	-	Local intervention indicated (e.g., oral antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death							
	ized by an infectious process involv			I	I							
Eye infection		Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated; enucleation	Death							
	ized by an infectious process involv	ring the eye.	ny erre et i	Life ii	L							
Gallbladder infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death							
Definition: A disorder character	ized by an infectious process involv	ring the gallbladder.	,									
Gum infection	Local therapy indicated (swish and swallow)	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death							
Definition: A disorder character	ized by an infectious process involv	ring the gums.										
Hepatic infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death							
Definition: A disorder character	ized by an infectious process involv	ring the liver.	1	·	'							
Hepatitis viral	Asymptomatic, treatment not indicated	-	Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis; reactivation of chronic hepatitis	Decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, coma)	Death							
Definition: A disorder character	ized by a viral pathologic process ir	nvolving the liver parenchyma.										
Infective myositis	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death							
Definition: A disorder character	ized by an infectious process involv	ing the skeletal muscles.										
Joint infection	-	Localized; local intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); needle aspiration indicated (single or multiple)	Arthroscopic intervention indicated (e.g., drainage) or arthrotomy (e.g., open surgical drainage)	Life-threatening consequences; urgent intervention indicated	Death							
Definition: A disorder character	ized by an infectious process involv	ring a joint.	<u> </u>	I								
Kidney infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death							

		Infections and infes	tations		
			Grade		
Adverse Event	1	2	3	4	5
_aryngitis	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder charac	terized by an inflammatory process in	nvolving the larynx.	1		
Lip infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	-	-
Definition: A disorder charac	terized by an infectious process invol	ving the lips.			
Lung infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder charac	terized by an infectious process invol	ving the lungs.			
Lymph gland infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder charac	terized by an infectious process invol	ving the lymph nodes.	T	T	
Mediastinal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder charac	terized by an infectious process invol	ving the mediastinum.			
Meningitis	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated; focal neurologic deficit	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder charac	terized by acute inflammation of the r	neninges of the brain and/or spinal	cord.	1	'
Mucosal infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder charac	terized by an infectious process invol	ving a mucosal surface.	T	T	
Nail infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	-	-
Definition: A disorder charac	terized by an infectious process invol	ving the nail.			
Otitis externa	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	terized by an infectious process invol	*	•	ive water exposure (swimmer's ea	r infection
Otitis media	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder charac	terized by an infectious process invol	ving the middle ear.	•	•	•
Ovarian infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative	Life-threatening consequences; urgent intervention indicated	Death

		Infections and infes	tations		
			Grade		
Adverse Event	1	2	3	4	5
Pancreas infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder character	rized by an infectious process involv	ing the pancreas.			
Papulopustular rash	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; lifethreatening consequences	Death
	rized by an eruption consisting of pa				p, and upper
Paronychia	is rash does not present with whiteh Nail fold edema or erythema; disruption of the cuticle	Localized intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	Surgical intervention or IV antibiotics indicated; limiting self care ADL	-	-
Definition: A disorder character	rized by an infectious process involv	ing the soft tissues around the nai	l.		
Pelvic infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder character	rized by an infectious process involv	ing the pelvic cavity.	T	T	
Penile infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder character	rized by an infectious process involv	ing the penis.			
Periorbital infection	rized by an infectious process involv	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Peripheral nerve infection	lized by an infectious process involv	Localized; local intervention	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
		indicated (e.g., topical antibiotic, antifungal, or antiviral)		urgent intervention indicated	Death
	rized by an infectious process involv	ing the peripheral herves.	N/ Albirdia Alf	l if the standard	D#
Peritoneal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder character	rized by an infectious process involv	ing the peritoneum.		1	
Pharyngitis	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder character	rized by inflammation of the throat.				
Phlebitis infective	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

		Infections and infes	tations		
			Grade		
Adverse Event	1	2	3	4	5
Definition: A disorder characterize of the infected vein.	ed by an infectious process involvi	ng the vein. Clinical manifestation	s include erythema, marked disco	mfort, swelling, and induration alo	ng the course
Pleural infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	ed by an infectious process involvi		ny erie et i	1.75 (1) (1)	Б "
Prostate infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by an infectious process involvi	ng the prostate gland.			
Rash pustular	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	-	-
Definition: A disorder characterize	ed by a circumscribed and elevate	d skin lesion filled with pus.			
Rhinitis infective	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	-	-	-
Definition: A disorder characterize	ed by an infectious process involvi	ng the nasal mucosal.		T	
Salivary gland infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by an infectious process involvi	ng the salivary gland.			
Scrotal infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by an infectious process involvi	ng the scrotum.			,
Sepsis	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by the presence of pathogenic	microorganisms in the blood strea	m that cause a rapidly progressing	g systemic reaction that may lead	to shock.
Sinusitis	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by an infectious process involvi	ng the mucous membranes of the	paranasal sinuses.	1	
Skin infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by an infectious process involvi	ng the skin.	T	T	
Small intestine infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by an infectious process involvi	ng the small intestine.	T	T	
Soft tissue infection		Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	ed by an infectious process involvi	ng soπ tissues.			
Splenic infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

Grade							
Adverse Event	1	2	3	4	5		
	ized by an infectious process involvi		3	4	5		
Stoma site infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder character	ized by an infectious process involvi	ing a stoma (surgically created op	ening on the surface of the body).	1			
Tooth infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder character	ized by an infectious process involving		1	1			
Tracheitis	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
	ized by an infectious process involving				1		
Upper respiratory infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder character	ized by an infectious process involving	ing the upper respiratory tract (no	se, paranasal sinuses, pharynx, la	rynx, or trachea).			
Urethral infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder character	ized by an infectious process involvi	ing the urethra.					
Urinary tract infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder character	ized by an infectious process involvi	ing the urinary tract, most commo	nly the bladder and the urethra.		,		
Uterine infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder character	ized by an infectious process involvi	ing the endometrium. It may exten	Id to the myometrium and parame	trial tissues.	,		
Vaginal infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder character	ized by an infectious process involving	ing the vagina.					
Vulval infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder character	ized by an infectious process involvi	ing the vulva.		1			
Wound infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder character	ized by an infectious process involving	ing the wound.	1	1			
Infections and infestations - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death		

	,,	, poisoning and procedu	Grade		
Adverse Event	1	2	3	4	5
Ankle fracture	Mild; non-surgical intervention	Limiting instrumental ADL;	Limiting self care ADL; elective	4	3
	indicated	operative intervention indicated	surgery indicated		-
Definition: A finding of damage t affected leg and foot.	o the ankle joint characterized by a	a break in the continuity of the ank	le bone. Symptoms include marke	d discomfort, swelling and difficult	y moving the
Aortic injury	_	_	Severe symptoms; limiting self	Life-threatening consequences;	Death
, ,			care ADL; disabling; repair or	evidence of end organ damage;	
			revision indicated	urgent operative intervention	
				indicated	
Definition: A finding of damage to			<u> </u>		l
Arterial injury	Asymptomatic diagnostic	Symptomatic (e.g., claudication); repair or revision	Severe symptoms; limiting self	Life-threatening consequences; evidence of end organ damage;	Death
	finding; intervention not indicated	not indicated	care ADL; disabling; repair or revision indicated	urgent operative intervention	
				indicated	
Definition: A finding of damage t	o an artery.				
Biliary anastomotic leak	Asymptomatic diagnostic	Symptomatic; medical	Severe symptoms; radiologic,	Life-threatening consequences;	Death
	observations only; intervention	intervention indicated	endoscopic or elective operative	urgent operative intervention	
	not indicated		intervention indicated	indicated	l
	f bile due to breakdown of a biliary				l
Bladder anastomotic leak	Asymptomatic diagnostic observations only; intervention	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative	Life-threatening consequences; urgent operative intervention	Death
	not indicated	intervention indicated	intervention indicated	indicated	
Definition: A finding of leakage of	f urine due to breakdown of a blad	। lder anastomosis (surgical connec	tion of two separate anatomic stru	ctures).	1
Bruising	Localized or in a dependent	Generalized	=	-	-
	area				
Definition: A finding of injury of the	ne soft tissues or bone characterize	ed by leakage of blood into surrou	nding tissues.	,	
Burn	Minimal symptoms; intervention	Medical intervention; minimal	Moderate to major debridement	Life-threatening consequences	Death
	not indicated	debridement indicated	or reconstruction indicated		
	integrity to the anatomic site of an			nicals, direct heat, electricity, flam	es and
	depends on the length and intensi			Life threatening concessions	Dooth
Dermatitis radiation	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation,	Moist desquamation in areas other than skin folds and	Life-threatening consequences; skin necrosis or ulceration of full	Death
	aooquamaton	mostly confined to skin folds	creases; bleeding induced by	thickness dermis; spontaneous	
		and creases; moderate edema	minor trauma or abrasion	bleeding from involved site; skin	
				graft indicated	
	s inflammatory reaction occurring a		T .		
Esophageal anastomotic leak	Asymptomatic diagnostic observations only; intervention	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative	Life-threatening consequences; urgent operative intervention	Death
	not indicated	intervention indicated	intervention indicated	indicated	
Definition: A finding of leakage d	ue to breakdown of an esophagea	l anastomosis (surgical connection	n of two separate anatomic structu	res).	1
Fall	Minor with no resultant injuries;	Symptomatic; noninvasive	Hospitalization indicated	-	-
	intervention not indicated	intervention indicated			
Definition: A finding of sudden m	ovement downward, usually result	ting in injury.	T	Γ	1
Fallopian tube anastomotic leak		Symptomatic; medical	Severe symptoms; radiologic,	Life-threatening consequences;	Death
	diagnostic observations only;	intervention indicated	endoscopic or elective operative intervention indicated	urgent operative intervention indicated	
Definition: A finding of leakage d	intervention not indicated ue to breakdown of a fallopian tub	e anastomosis (surgical connection	1	l	l
Fallopian tube perforation	Asymptomatic diagnostic	Symptomatic and intervention	Severe symptoms; elective	Life-threatening consequences;	Death
i allopiari tube perioration	observations only; intervention	not indicated	operative intervention indicated	urgent operative intervention	Death
	not indicated			indicated (e.g., organ resection)	
Definition: A finding of rupture of	the fallopian tube wall.				
Fracture	Asymptomatic; clinical or	Symptomatic but non-displaced;	Severe symptoms; displaced or	Life-threatening consequences;	Death
	diagnostic observations only;	immobilization indicated	open wound with bone	urgent intervention indicated	
	intervention not indicated		exposure; disabling; operative		1
			intervention indicated		

Grade							
Adverse Event	1	2	3	4	5		
Gastric anastomotic leak	Asymptomatic diagnostic	Symptomatic; medical	Severe symptoms; radiologic,		Death		
Gastric ariastorriotic leak	observations only; intervention	intervention indicated	endoscopic or elective operative	Life-threatening consequences; urgent operative intervention	Dealii		
	not indicated	intervention indicated	intervention indicated	indicated			
Definition: A finding of lookens d	ı	tomonia (oursiaal connection of tu	1	maloatoa	1		
	ue to breakdown of a gastric anas			I	I		
Gastrointestinal anastomotic	Asymptomatic diagnostic	Symptomatic; medical	Severe symptoms; radiologic,	Life-threatening consequences;	Death		
leak	observations only; intervention	intervention indicated	endoscopic or elective operative	urgent operative intervention			
	not indicated	l	intervention indicated	indicated	l		
Definition: A finding of leakage d	ue to breakdown of a gastrointesti	nal anastomosis (surgical connect	tion of two separate anatomic struc	ctures).			
Gastrointestinal stoma necrosis	-	Superficial necrosis;	Severe symptoms;	Life-threatening consequences;	Death		
		intervention not indicated	hospitalization or elective	urgent intervention indicated			
			operative intervention indicated				
Definition: A finding of a necrotic	process occurring in the gastroint	estinal tract stoma.					
Hip fracture	-	Hairline fracture; mild pain;	Severe pain; hospitalization or	Life-threatening consequences;	-		
		limiting instrumental ADL; non-	intervention indicated for pain	symptoms associated with			
		surgical intervention indicated	control (e.g., traction); operative	neurovascular compromise			
			intervention indicated				
Definition: A finding of traumatic	injury to the hip in which the contir	nuity of either the femoral head, fe	moral neck, intertrochanteric or su	btrochanteric regions is broken.			
Injury to carotid artery	-	-	Severe symptoms; limiting self	Life-threatening consequences;	Death		
, a., to ourous artory			care ADL (e.g., transient	urgent intervention indicated	Doain		
			cerebral ischemia); repair or	January Strate Midioatod			
			revision indicated				
Definition: A finding of damage to	the carotid artery.	ı	1	ı	'		
Injury to inferior vena cava				Life-threatening consequences;	Death		
injury to interior veria cava	-	-	-	urgent intervention indicated	Death		
D-6-iti	 	l	I	argent intervention indicated	1		
Definition: A finding of damage to	the interior vena cava.		1				
Injury to jugular vein	-	-	Symptomatic limiting self care	Life-threatening consequences;	Death		
			ADL; disabling; repair or	urgent intervention indicated			
		I	revision indicated	I			
Definition: A finding of damage to	the jugular vein.						
	1	1		1			
Injury to superior vena cava	Asymptomatic diagnostic	Symptomatic; repair or revision	Severe symptoms; limiting self	Life-threatening consequences;	Death		
Injury to superior vena cava		Symptomatic; repair or revision not indicated	Severe symptoms; limiting self care ADL; disabling; repair or	Life-threatening consequences; evidence of end organ damage;	Death		
Injury to superior vena cava	Asymptomatic diagnostic				Death		
Injury to superior vena cava	Asymptomatic diagnostic finding; intervention not		care ADL; disabling; repair or	evidence of end organ damage;	Death		
Injury to superior vena cava Definition: A finding of damage to	Asymptomatic diagnostic finding; intervention not indicated		care ADL; disabling; repair or	evidence of end organ damage; urgent operative intervention	Death		
	Asymptomatic diagnostic finding; intervention not indicated		care ADL; disabling; repair or	evidence of end organ damage; urgent operative intervention	Death		
Definition: A finding of damage to	Asymptomatic diagnostic finding; intervention not indicated	not indicated	care ADL; disabling; repair or revision indicated	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences;			
Definition: A finding of damage to	Asymptomatic diagnostic finding; intervention not indicated the superior vena cava. Asymptomatic diagnostic	not indicated Symptomatic; medical	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic,	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences;			
Definition: A finding of damage to	Asymptomatic diagnostic finding; intervention not indicated the superior vena cava. Asymptomatic diagnostic observations only; intervention	not indicated Symptomatic; medical intervention indicated	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention			
Definition: A finding of damage to Intestinal stoma leak Definition: A finding of leakage o	Asymptomatic diagnostic finding; intervention not indicated the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (surgically created opening on the	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body).	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A finding of damage to	Asymptomatic diagnostic finding; intervention not indicated the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated	not indicated Symptomatic; medical intervention indicated	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body). Severe symptoms; IV fluids,	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences;			
Definition: A finding of damage to Intestinal stoma leak Definition: A finding of leakage o	Asymptomatic diagnostic finding; intervention not indicated the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (surgically created opening on the Self-limited; intervention not	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body). Severe symptoms; IV fluids, tube feeding, or TPN indicated	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A finding of damage to Intestinal stoma leak Definition: A finding of leakage o	Asymptomatic diagnostic finding; intervention not indicated the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (surgically created opening on the Self-limited; intervention not	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body). Severe symptoms; IV fluids,	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention	Death		
Definition: A finding of damage to Intestinal stoma leak Definition: A finding of leakage of Intestinal stoma obstruction	Asymptomatic diagnostic finding; intervention not indicated the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (surgically created opening on the Self-limited; intervention not indicated	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body). Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention	Death		
Definition: A finding of damage to Intestinal stoma leak Definition: A finding of leakage of Intestinal stoma obstruction Definition: A finding of blockage of Intestinal stoma obstruction	Asymptomatic diagnostic finding; intervention not indicated the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated f contents from an intestinal stoma	Symptomatic; medical intervention indicated (surgically created opening on the Self-limited; intervention not indicated of the intestinal stoma.	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body). Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A finding of damage to Intestinal stoma leak Definition: A finding of leakage of Intestinal stoma obstruction	Asymptomatic diagnostic finding; intervention not indicated of the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated frontents from an intestinal stomatic formula of the normal flow of the contents of Minimal bleeding identified on	Symptomatic; medical intervention indicated (surgically created opening on the Self-limited; intervention not indicated of the intestinal stoma. Moderate bleeding; medical	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body). Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated Severe bleeding; transfusion	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A finding of damage to Intestinal stoma leak Definition: A finding of leakage of Intestinal stoma obstruction Definition: A finding of blockage of Intestinal stoma obstruction	Asymptomatic diagnostic finding; intervention not indicated the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated f contents from an intestinal stoma	Symptomatic; medical intervention indicated (surgically created opening on the Self-limited; intervention not indicated of the intestinal stoma.	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body). Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated Severe bleeding; transfusion indicated; radiologic or	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A finding of damage to Intestinal stoma leak Definition: A finding of leakage of Intestinal stoma obstruction Definition: A finding of blockage of Intestinal stoma obstruction	Asymptomatic diagnostic finding; intervention not indicated the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated f contents from an intestinal stomatic of the normal flow of the contents of the increase of the i	Symptomatic; medical intervention indicated (surgically created opening on the Self-limited; intervention not indicated of the intestinal stoma. Moderate bleeding; medical	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body). Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated Severe bleeding; transfusion	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A finding of damage to Intestinal stoma leak Definition: A finding of leakage of Intestinal stoma obstruction Definition: A finding of blockage of Intestinal stoma site bleeding	Asymptomatic diagnostic finding; intervention not indicated of the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated f contents from an intestinal stomatic from the normal flow of the contents of the normal flow of	Symptomatic; medical intervention indicated (surgically created opening on the Self-limited; intervention not indicated of the intestinal stoma. Moderate bleeding; medical	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body). Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated Severe bleeding; transfusion indicated; radiologic or endoscopic intervention	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A finding of damage to Intestinal stoma leak Definition: A finding of leakage of Intestinal stoma obstruction Definition: A finding of blockage of Intestinal stoma site bleeding Definition: A finding of blood leak	Asymptomatic diagnostic finding; intervention not indicated the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated f contents from an intestinal stoma - of the normal flow of the contents of the normal flow of the contents from the indicated on clinical exam; intervention not indicated	Symptomatic; medical intervention indicated (surgically created opening on the Self-limited; intervention not indicated of the intestinal stoma. Moderate bleeding; medical intervention indicated	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body). Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated	Death Death		
Definition: A finding of damage to Intestinal stoma leak Definition: A finding of leakage of Intestinal stoma obstruction Definition: A finding of blockage of Intestinal stoma site bleeding	Asymptomatic diagnostic finding; intervention not indicated the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated f contents from an intestinal stoma - of the normal flow of the contents of the normal flow of the contents from the intervention not indicated with the contents of the normal flow of the normal flow of the contents of the normal flow of the normal	Symptomatic; medical intervention indicated (surgically created opening on the Self-limited; intervention not indicated of the intestinal stoma. Moderate bleeding; medical intervention indicated	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body). Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated Complete resection or	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A finding of damage to Intestinal stoma leak Definition: A finding of leakage of Intestinal stoma obstruction Definition: A finding of blockage of Intestinal stoma site bleeding Definition: A finding of blood leak	Asymptomatic diagnostic finding; intervention not indicated the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated f contents from an intestinal stoma - of the normal flow of the contents of the normal flow of the contents from the indicated on clinical exam; intervention not indicated	Symptomatic; medical intervention indicated (surgically created opening on the Self-limited; intervention not indicated of the intestinal stoma. Moderate bleeding; medical intervention indicated	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body). Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated Complete resection or reconstruction of injured	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated	Death Death		
Definition: A finding of damage to Intestinal stoma leak Definition: A finding of leakage of Intestinal stoma obstruction Definition: A finding of blockage of Intestinal stoma site bleeding Definition: A finding of blood leak	Asymptomatic diagnostic finding; intervention not indicated the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated f contents from an intestinal stoma - of the normal flow of the contents of the normal flow of the contents from the intervention not indicated with the contents of the normal flow of the normal flow of the contents of the normal flow of the normal	Symptomatic; medical intervention indicated (surgically created opening on the Self-limited; intervention not indicated of the intestinal stoma. Moderate bleeding; medical intervention indicated	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body). Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated Complete resection or reconstruction of injured organ/structure indicated;	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated	Death Death		
Definition: A finding of damage to Intestinal stoma leak Definition: A finding of leakage of Intestinal stoma obstruction Definition: A finding of blockage of Intestinal stoma site bleeding Definition: A finding of blood leak Intraoperative arterial injury	Asymptomatic diagnostic finding; intervention not indicated the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated f contents from an intestinal stoma - of the normal flow of the contents of Minimal bleeding identified on clinical exam; intervention not indicated age from the intestinal stoma. Primary repair of injured organ/structure indicated	Symptomatic; medical intervention indicated (surgically created opening on the Self-limited; intervention not indicated of the intestinal stoma. Moderate bleeding; medical intervention indicated Partial resection of injured organ/structure indicated	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body). Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated Complete resection or reconstruction of injured	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated	Death Death		
Definition: A finding of damage to Intestinal stoma leak Definition: A finding of leakage of Intestinal stoma obstruction Definition: A finding of blockage of Intestinal stoma site bleeding Definition: A finding of blood leak Intraoperative arterial injury Definition: A finding of damage to	Asymptomatic diagnostic finding; intervention not indicated the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated f contents from an intestinal stoma - of the normal flow of the contents of the normal flow of the contents on clinical exam; intervention not indicated age from the intestinal stoma. Primary repair of injured organ/structure indicated on an artery during a surgical process.	Symptomatic; medical intervention indicated (surgically created opening on the Self-limited; intervention not indicated of the intestinal stoma. Moderate bleeding; medical intervention indicated Partial resection of injured organ/structure indicated dure.	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body). Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated Complete resection or reconstruction of injured organ/structure indicated; disabling	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent intervention indicated Life-threatening consequences; urgent intervention indicated	Death Death Death		
Definition: A finding of damage to Intestinal stoma leak Definition: A finding of leakage of Intestinal stoma obstruction Definition: A finding of blockage of Intestinal stoma site bleeding Definition: A finding of blood leak Intraoperative arterial injury	Asymptomatic diagnostic finding; intervention not indicated the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated f contents from an intestinal stoma - off the normal flow of the contents of the normal flow of the contents from an intestinal stoma dinicated stage from the intervention not indicated age from the intestinal stoma. Primary repair of injured organ/structure indicated an artery during a surgical procesure.	Symptomatic; medical intervention indicated (surgically created opening on the Self-limited; intervention not indicated of the intestinal stoma. Moderate bleeding; medical intervention indicated Partial resection of injured organ/structure indicated dure. Partial resection of injured	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body). Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated Complete resection or reconstruction of injured organ/structure indicated; disabling	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent intervention indicated Life-threatening consequences; urgent intervention indicated	Death Death		
Definition: A finding of damage to Intestinal stoma leak Definition: A finding of leakage of Intestinal stoma obstruction Definition: A finding of blockage of Intestinal stoma site bleeding Definition: A finding of blood leak Intraoperative arterial injury Definition: A finding of damage to	Asymptomatic diagnostic finding; intervention not indicated the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated f contents from an intestinal stoma - of the normal flow of the contents of the normal flow of the contents on clinical exam; intervention not indicated age from the intestinal stoma. Primary repair of injured organ/structure indicated on an artery during a surgical process.	Symptomatic; medical intervention indicated (surgically created opening on the Self-limited; intervention not indicated of the intestinal stoma. Moderate bleeding; medical intervention indicated Partial resection of injured organ/structure indicated dure.	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body). Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated Complete resection or reconstruction of injured organ/structure indicated; disabling	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent intervention indicated Life-threatening consequences; urgent intervention indicated	Death Death Death		

		, poisoning and proced	Grade		
Adverse Event	1	2	3	4	5
	o the breast parenchyma during a		•	7	
Intraoperative cardiac injury	-	-	Primary repair of injured organ/structure indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to	o the heart during a surgical proce	dure.			
Intraoperative ear injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection of injured organ/structure indicated; disabling (e.g., impaired hearing; impaired balance)	Life-threatening consequences; urgent intervention indicated	Death
	o the ear during a surgical procedu		Ta	1	
Intraoperative endocrine injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to	o the endocrine gland during a sur	gical procedure.			
Intraoperative gastrointestinal injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to	o the gastrointestinal system durin	g a surgical procedure.			
Intraoperative head and neck injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to	o the head and neck during a surg	ical procedure.			
Intraoperative hemorrhage	-	-	Postoperative radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of uncontroll	ed bleeding during a surgical prod	edure.	•	·	
Intraoperative hepatobiliary injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to	o the hepatic parenchyma and/or l	oiliary tract during a surgical pro	cedure.		
Intraoperative musculoskeletal injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
	o the musculoskeletal system duri				
Intraoperative neurological injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
	o the nervous system during a sur		0	l :f- 4b4i	D41-
Intraoperative ocular injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
	o the eye during a surgical proced			1	
Intraoperative renal injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to	o the kidney during a surgical prod	edure.			
Intraoperative reproductive tract injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured	Life-threatening consequences; urgent intervention indicated	Death

	Injury	, poisoning and procedu	•					
	Grade 4 2 2 4 5							
Adverse Event	1	2	3	4	5			
	o the reproductive organs during a	1						
Intraoperative respiratory injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A finding of damage to	o the respiratory system during a s	urgical procedure.	1 0	I	1			
Intraoperative skin injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A finding of damage to	o the skin during a surgical proced	ure.	•					
Intraoperative splenic injury	-	Primary repair of injured organ/structure indicated	Resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A finding of damage to	o the spleen during a surgical prod		T	T				
Intraoperative urinary injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death			
	o the urinary system during a surg	T .	I	I	I			
Intraoperative venous injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A finding of damage to	o a vein during a surgical procedu	e.	T					
Kidney anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A finding of leakage o	f urine due to breakdown of a kidn	ey anastomosis (surgical connecti	on of two separate anatomic struc	tures).	•			
Large intestinal anastomotic leak	Asymptomatic diagnostic observations only; intervention	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative	Life-threatening consequences; urgent operative intervention	Death			
Deficitions A finding of looks and	not indicated	 	intervention indicated	indicated	l			
Pancreatic anastomotic leak	ue to breakdown of an anastomos	Symptomatic; medical			Death			
rancieanc anasiomone leak	Asymptomatic diagnostic observations only; intervention not indicated	intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Dealli			
Definition: A finding of leakage d	ue to breakdown of a pancreatic a	nastomosis (surgical connection o	f two separate anatomic structures	s).				
Pharyngeal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated		Death			
Definition: A finding of leakage d	ue to breakdown of a pharyngeal	anastomosis (surgical connection	of two separate anatomic structure	es).				
Postoperative hemorrhage	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; radiologic, endoscopic, or operative intervention indicated	Transfusion indicated of >=2 units (10 cc/kg for pediatrics) pRBCs beyond protocol specification; urgent radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A finding of bleeding of	occurring after a surgical procedur	e. T	T	Γ				
Postoperative thoracic procedure complication	-	Extubated within 24 - 72 hrs postoperatively	Extubated >72 hrs postoperatively, but before tracheostomy indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death			
Definition: A finding of a previous	sly undocumented problem that oc	curs after a thoracic procedure.	T	Γ				
Prolapse of intestinal stoma	Asymptomatic; reducible	Recurrent after manual reduction; local irritation or stool leakage; difficulty to fit appliance; limiting instrumental	Severe symptoms; elective operative intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death			

			Grade							
Adverse Event	1	2	3	4	5					
Definition: A finding of protrusion	of the intestinal stoma (surgically	created opening on the surface of	the body) above the abdominal su	urface.						
Prolapse of urostomy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Local care or maintenance; minor revision indicated	Dysfunctional stoma; elective operative intervention or major stomal revision indicated	Life-threatening consequences; urgent intervention indicated	Death					
Definition: A finding of displacem	ent of the urostomy.									
Radiation recall reaction (dermatologic)	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death					
	inflammatory reaction caused by		-	lowing radiotherapy. The inflamma	tory react					
· · · · · · · · · · · · · · · · · · ·	liated skin and the symptoms disa	i i								
Rectal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death					
Definition: A finding of leakage d	ue to breakdown of a rectal anasto	omosis (surgical connection of two	separate anatomic structures).	T						
Seroma	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; simple aspiration indicated	Symptomatic, elective radiologic or operative intervention indicated	-	-					
Definition: A finding of tumor-like	collection of serum in the tissues.									
Small intestinal anastomotic eak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death					
Definition: A finding of leakage d	ue to breakdown of an anastomos	is (surgical connection of two sepa	arate anatomic structures) in the sr	mall bowel.						
Spermatic cord anastomotic eak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death					
Definition: A finding of leakage d	ue to breakdown of a spermatic co	ord anastomosis (surgical connecti	on of two separate anatomic struc	tures).						
Spinal fracture	Mild back pain; nonprescription analgesics indicated	Moderate back pain; prescription analgesics indicated; limiting instrumental ADL	Severe back pain; hospitalization or intervention indicated for pain control (e.g., vertebroplasty); limiting self care ADL; disability	Life-threatening consequences; symptoms associated with neurovascular compromise	Death					
Definition: A finding of traumatic	injury to the spine in which the cor	itinuity of a vertebral bone is broke	en.	1	•					
Stenosis of gastrointestinal stoma	-	Symptomatic; IV fluids indicated <24 hrs; manual dilation at bedside	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death					
	of the gastrointestinal stoma (surg									
Stomal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	-	-					
Definition: A disorder characteriz	ed by a circumscribed, inflammato	ory and necrotic erosive lesion on t	he jejunal mucosal surface close t	to the anastomosis site following a						
Tracheal hemorrhage	Minimal bleeding identified on	Moderate bleeding; medical	Severe bleeding; transfusion	Life-threatening consequences;	Death					
·	clinical or diagnostic exam; intervention not indicated	intervention indicated	indicated; radiologic or endoscopic intervention indicated	urgent intervention indicated	20011					
Definition: A finding of bleeding f			1	l						
Tracheal obstruction	Partial asymptomatic obstruction on examination (e.g., visual, radiologic or endoscopic)	Symptomatic (e.g., noisy airway breathing), no respiratory distress; medical intervention indicated (e.g., steroids); limiting	Stridor; radiologic or endoscopic intervention indicated (e.g., stent, laser); limiting self care ADL	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death					

			Grade		
Adverse Event	1	2	3	4	5
Tracheostomy site bleeding	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of blood lea	kage from the tracheostomy site.				
Ureteric anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
	lue to breakdown of a ureteral ana				
Jrethral anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage o	lue to breakdown of a urethral ana	stomosis (surgical connection of tw	vo separate anatomic structures).		
Urostomy leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of	of contents from a urostomy.				1
Urostomy obstruction	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; dilation or endoscopic repair or stent placement indicated	Altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); elective operative intervention indicated	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
Definition: A finding of blockage	of the urostomy.	T.			
Urostomy site bleeding	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of bleeding	from the urostomy site.	'	,	•	•
Urostomy stenosis	-	Symptomatic but no hydronephrosis, no sepsis or no renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic (e.g., hydronephrosis, or renal dysfunction); elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of narrowing	of the opening of a urostomy.	,	•	•	
Uterine anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage o	lue to breakdown of a uterine anas	tomosis (surgical connection of tw	o separate anatomic structures).		
Uterine perforation	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	zed by a rupture in the uterine wall.		Cause aumentama, radialagia	Life threatening concessions	Dooth
/aginal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage o	lue to breakdown of a vaginal anas	tomosis (surgical connection of tw	o separate anatomic structures).		
/as deferens anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of	lue to breakdown of a vas deferens	s anastomosis (surgical connection	n of two separate anatomic structu	res).	
Vascular access complication	-	Device dislodgement, blockage, leak, or malposition; device replacement indicated	Deep vein or cardiac thrombosis; intervention indicated (e.g., anticoagulation, lysis, filter, invasive procedure)	Embolic event including pulmonary embolism or life-threatening thrombus	Death

	Injury	, poisoning and procedu	ral complications		
			Grade		
Adverse Event	1	2	3	4	5
Venous injury	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); repair or revision not indicated	Severe symptoms; limiting self care ADL; repair or revision indicated; disabling	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to	a vein.				
Wound complication	Incisional separation of <=25% of wound, no deeper than superficial fascia	Incisional separation >25% of wound; local care indicated	Hernia without evidence of strangulation; fascial disruption/dehiscence; primary wound closure or revision by operative intervention indicated	Hernia with evidence of strangulation; major reconstruction flap, grafting, resection, or amputation indicated	Death
	Incisional separation of <=25%		Fascial disruption or dehiscence	Life threatening concessions	Dooth
Wound dehiscence	Incisional separation of <=25% of wound, no deeper than superficial fascia	Incisional separation >25% of wound with local care; asymptomatic hernia or symptomatic hernia without evidence of strangulation	Fascial disruption or deniscence without evisceration; primary wound closure or revision by operative intervention indicated	Life-threatening consequences; symptomatic hernia with evidence of strangulation; fascial disruption with evisceration; major reconstruction flap, grafting, resection, or amputation indicated	Death
Definition: A finding of separation	of the approximated margins of a	surgical wound.	T	T	1
Wrist fracture	Mild; non-surgical intervention indicated	Limiting instrumental ADL; operative intervention indicated	Limiting self care ADL; elective surgery indicated	-	-
Definition: A finding of traumatic i	injury to the wrist joint in which the	continuity of a wrist bone is broke	en.		
Injury, poisoning and procedural complications - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

	Investigations								
			Grade		_				
Adverse Event	1	2	3	4	5				
Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage	-	-				
		romboplastin time is found to be g s and disorders, both primary and		possible indicator of coagulopat	hy, a prolonged				
Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-				
Definition: A finding based on lab	oratory test results that indicate a	। n increase in the level of alanine a	ı minotransferase (ALT or SGPT) ir	n the blood specimen.					
Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-				
Definition: A finding based on lab	oratory test results that indicate a	n increase in the level of alkaline p	hosphatase in a blood specimen.	'	'				
Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-				
Definition: A finding based on lab	oratory test results that indicate a	n increase in the level of aspartate	aminotransferase (AST or SGOT) in a blood specimen.	•				
Blood antidiuretic hormone abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Hospitalization indicated	-	-				
Definition: A finding based on lab	oratory test results that indicate a	bnormal levels of antidiuretic horm	one in the blood specimen.						
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN	-				
Definition: A finding based on lab	oratory test results that indicate a	n abnormally high level of bilirubin	in the blood. Excess bilirubin is a	ssociated with jaundice.					
Blood corticotrophin decreased	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Hospitalization indicated	-	-				
Definition: A finding based on lab	oratory test results that indicate a	n decrease in levels of corticotropl	nin in a blood specimen.						
Blood gonadotrophin abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-				
Definition: A finding based on lab	oratory test results that indicate a	, bnormal levels of gonadotrophin h	ormone in a blood specimen.	'	'				
Blood prolactin abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	-	-	-				
Definition: A finding based on lab	ı	l bnormal levels of prolactin hormor	l ne in a blood specimen	I	ı				
Carbon monoxide diffusing		6 - 8 units below LLN; for follow-	Asymptomatic decrease of >8	_	Τ.				
capacity decreased	up, a decrease of 3 - 5 units (ml/min/mm Hg) below the baseline value	up, an asymptomatic decrease of >5 - 8 units (ml/min/mm Hg) below the baseline value	units drop; >5 units drop along with the presence of pulmonary symptoms (e.g., >Grade 2 hypoxia or >Grade 2 or higher dyspnea)						
Definition: A finding based on lun	g function test results that indicate	a decrease in the lung capacity	to absorb carbon monoxide.						
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer	-	-				
Definition: A laboratory test result		of cardiac troponin I in a biologica		<u> </u>					
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer	-	-				
Definition: A laboratory test result	which indicates increased levels	of cardiac troponin T in a biologica	al specimen.						
CD4 lymphocytes decreased	<lln -="" 0.5="" 500="" <lln="" mm3;="" x<br="">10e9 /L</lln>	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200 - 50/mm3; <0.2 x 0.05 - 10e9 /L	<50/mm3; <0.05 x 10e9 /L	-				
Definition: A finding based on lab	oratory test results that indicate a	n decrease in levels of CD4 lymph	ocytes in a blood specimen.						
Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L	-				
Definition: A finding based on lab	oratory test results that indicate h	igher than normal levels of choles	erol in a blood specimen.		_				
CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN psphokinase in a blood specimen.	>10 x ULN	-				

		Investigations	5		
			Grade		
Adverse Event	1	2	3	4	5
Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	-
Definition: A finding based on lab	oratory test results that indicate in	creased levels of creatinine in a b	iological specimen.		
Ejection fraction decreased	-	Resting ejection fraction (EF) 50 - 40%; 10 - 19% drop from baseline	Resting ejection fraction (EF) 39 - 20%; >20% drop from baseline	Resting ejection fraction (EF) <20%	-
Definition: The percentage compo	uted when the amount of blood eje	ected during a ventricular contracti	ion of the heart is compared to the	amount that was present prior to	the
Electrocardiogram QT corrected interval prolonged		QTc 481 - 500 ms	QTc >= 501 ms on at least two separate ECGs	QTc >= 501 or >60 ms change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	-
Definition: A finding of a cardiac of	dysrhythmia characterized by an a	bnormally long corrected QT inter	val.	<u> </u>	
Fibrinogen decreased	<1.0 - 0.75 x LLN or <25% decrease from baseline	<0.75 - 0.5 x LLN or 25 - <50% decrease from baseline	<0.5 - 0.25 x LLN or 50 - <75% decrease from baseline	<0.25 x LLN or 75% decrease from baseline or absolute value <50 mg/dL	-
Definition: A finding based on lab	oratory test results that indicate a	n decrease in levels of fibrinogen i	in a blood specimen.		,
Forced expiratory volume decreased	FEV1% (percentages of observed FEV1 and FVC related to their respective predicted values) 99 - 70% predicted	FEV1 60 - 69%	50 - 59%	<= 49%	-
Definition: A finding based on tes	t results that indicate a relative de	crease in the fraction of the forced	vital capacity that is exhaled in a	specific number of seconds.	
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on lab	oratory test results that indicate hi	gher than normal levels of the enz	zyme gamma-glutamyltransferase	in the blood specimen. GGT (gam	ıma-
glutamyltransferase) catalyzes th	ne transfer of a gamma glutamyl g	roup from a gamma glutamyl pept	ide to another peptide, amino acid	s or water.	
Growth hormone abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	-	-	-
Definition: A finding based on lab	oratory test results that indicate al	onormal levels of growth hormone	in a biological specimen.		
Haptoglobin decreased	<lln< td=""><td>-</td><td>-</td><td>-</td><td>-</td></lln<>	-	-	-	-
Definition: A finding based on lab	oratory test results that indicate a	r n decrease in levels of haptoglobir	n in a blood specimen.	ı	'
Hemoglobin increased	Increase in >0 - 2 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN	-	-
Definition: A finding based on lab	oratory test results that indicate in	creased levels of hemoglobin in a	biological specimen.		
INR increased	>1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation	-	-
Definition: A finding based on lab	oratory test results that indicate a	n increase in the ratio of the patier	nt's prothrombin time to a control s	ample in the blood.	
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN	-
Definition: A finding based on lab	oratory test results that indicate a	n increase in the level of lipase in	a biological specimen.		
_ymphocyte count decreased	<lln -="" 0.8="" 800="" <lln="" mm3;="" x<br="">10e9 /L</lln>	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	-
Definition: A finding based on lab	oratory test results that indicate a	decrease in number of lymphocyt	es in a blood specimen.		
ymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	-
Definition: A finding based on lab	oratory test results that indicate a	abnormal increase in the numbe	r of lymphocytes in the blood, effu	sions or bone marrow.	•
Neutrophil count decreased	<lln -="" 1.5="" 1500="" <lln="" mm3;="" x<br="">10e9 /L</lln>	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L		<500/mm3; <0.5 x 10e9 /L	-
Definition: A finding based on lab	oratory test results that indicate a	decrease in number of neutrophils	s in a blood specimen.		
Pancreatic enzymes decreased	<lln and="" asymptomatic<="" td=""><td>Increase in stool frequency, bulk, or odor; steatorrhea</td><td>Sequelae of absorption deficiency</td><td>-</td><td>-</td></lln>	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency	-	-
Definition: A finding based on lab	oratory test results that indicate a	ı	enzymes in a biological specimen	•	•

	Investigations									
	Grade									
Adverse Event	1	2	3	4	5					
Platelet count decreased	<lln -="" -<="" 75,000="" <lln="" mm3;="" td=""><td><75,000 - 50,000/mm3; <75.0 -</td><td><50,000 - 25,000/mm3; <50.0 -</td><td><25,000/mm3; <25.0 x 10e9 /L</td><td>-</td></lln>	<75,000 - 50,000/mm3; <75.0 -	<50,000 - 25,000/mm3; <50.0 -	<25,000/mm3; <25.0 x 10e9 /L	-					
	75.0 x 10e9 /L	50.0 x 10e9 /L	25.0 x 10e9 /L							
Definition: A finding based on lab	oratory test results that indicate a	decrease in number of platelets in	a blood specimen.							
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN	-					
Definition: A finding based on lab	oratory test results that indicate a	n increase in the levels of amylase	in a serum specimen.							
Urine output decreased	-	-	Oliguria (<80 ml in 8 hr)	Anuria (<240 ml in 24 hr)	-					
Definition: A finding based on tes	t results that indicate urine produc	tion is less relative to previous ou	tput.							
Vital capacity abnormal	90 - 75% of predicted value	<75 - 50% of predicted value;	<50% of predicted value;	-	-					
		limiting instrumental ADL	limiting self care ADL							
Definition: A finding based on pul	lmonary function test results that in	ndicate an abnormal vital capacity	(amount of exhaled after a maxim	num inhalation) when compared to	the predicted					
value.	T	I	r	T	T					
Weight gain	5 - <10% from baseline	10 - <20% from baseline	>=20% from baseline	-	-					
Definition: A finding characterized	by an increase in overall body w	eight; for pediatrics, greater than t	he baseline growth curve.							
Weight loss	5 to <10% from baseline;	10 - <20% from baseline;	>=20% from baseline; tube	-	-					
	intervention not indicated	nutritional support indicated	feeding or TPN indicated							
Definition: A finding characterized	d by a decrease in overall body we	eight; for pediatrics, less than the b	paseline growth curve.							
White blood cell decreased	<lln -="" 3.0="" 3000="" <lln="" mm3;="" td="" x<=""><td>,</td><td><2000 - 1000/mm3; <2.0 - 1.0 x</td><td><1000/mm3; <1.0 x 10e9 /L</td><td>-</td></lln>	,	<2000 - 1000/mm3; <2.0 - 1.0 x	<1000/mm3; <1.0 x 10e9 /L	-					
	10e9 /L	10e9 /L	10e9 /L							
Definition: A finding based on lab	oratory test results that indicate a	n decrease in number of white blo	od cells in a blood specimen.	T	1					
Investigations - Other, specify	Asymptomatic or mild	Moderate; minimal, local or	Severe or medically significant	Life-threatening consequences;	Death					
	, , ,	noninvasive intervention	but not immediately life-	urgent intervention indicated						
	observations only; intervention not indicated	indicated; limiting age- appropriate instrumental ADL	threatening; hospitalization or prolongation of existing							
	not muicateu	appropriate instrumental ADL	hospitalization indicated;							
			disabling; limiting self care ADL							

		Metabolism and nutrition	Grade		
Adverse Event	1	2	Grade 3	4	5
Acidosis	pH <normal, but="">=7.3</normal,>	2	pH <7.3	Life-threatening consequences	Death
	1.	h hydrogon ion concentration) of t	II.	Life-tiffeatering consequences	Deali
	erized by abnormally high acidity (high	T i i i i i i i i i i i i i i i i i i i		Life threatening concession	Death
Alcohol intolerance	-	Present	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	erized by an increase in sensitivity to	I the adverse effects of alcohol wh	1		i nausea
omiting, indigestion and head		and daverse emotes of discriot, with	on our morade natur congestion,	omir naonoo, noare ayomyanmao, i	iaaooa,
Alkalosis	pH >normal, but <=7.5	-	pH >7.5	Life-threatening consequences	Death
Definition: A disorder characte	erized by abnormally high alkalinity (lo	ow hydrogen-ion concentration) of	the blood and other body tissues.		'
Anorexia	Loss of appetite without	Oral intake altered without	Associated with significant	Life-threatening consequences;	Death
anor ovace	alteration in eating habits	significant weight loss or	weight loss or malnutrition (e.g.,	urgent intervention indicated	Dou
		malnutrition; oral nutritional	inadequate oral caloric and/or		
		supplements indicated	fluid intake); tube feeding or		
			TPN indicated		
Definition: A disorder characte	erized by a loss of appetite.	T	T	Т	
Dehydration	Increased oral fluids indicated;	IV fluids indicated <24 hrs	IV fluids or hospitalization	Life-threatening consequences;	Death
	dry mucous membranes;		indicated	urgent intervention indicated	
5 6 W A P 1 1 4	diminished skin turgor			l	I
	erized by excessive loss of water from				I
Glucose intolerance	Asymptomatic; clinical or	Symptomatic; dietary	Severe symptoms; insulin	Life-threatening consequences;	Death
	diagnostic observations only; intervention not indicated	modification or oral agent indicated	indicated	urgent intervention indicated	
Definition: A disorder characte	erized by an inability to properly meta	1	I	ļ	l
Hypercalcemia	Corrected serum calcium of	Corrected serum calcium of	Corrected serum calcium of	Corrected serum calcium of	Death
туретсатсетна	>ULN - 11.5 mg/dL; >ULN - 2.9	>11.5 - 12.5 mg/dL; >2.9 - 3.1	>12.5 - 13.5 mg/dL; >3.1 - 3.4	>13.5 mg/dL; >3.4 mmol/L;	Death
	mmol/L; Ionized calcium >ULN		mmol/L; Ionized calcium >1.6 -	lonized calcium >1.8 mmol/L;	
	- 1.5 mmol/L	1.6 mmol/L; symptomatic	1.8 mmol/L; hospitalization	life-threatening consequences	
			indicated		
Definition: A disorder characte	erized by laboratory test results that in	ndicate an elevation in the concen	tration of calcium (corrected for all	oumin) in blood.	
Hyperglycemia	Fasting glucose value >ULN -	Fasting glucose value >160 -	>250 - 500 mg/dL; >13.9 - 27.8	>500 mg/dL; >27.8 mmol/L; life-	Death
	160 mg/dL; Fasting glucose	250 mg/dL; Fasting glucose	mmol/L; hospitalization	threatening consequences	
5 6 W A P I I I	value >ULN - 8.9 mmol/L	value >8.9 - 13.9 mmol/L	indicated		١ .
Definition: A disorder characte ntolerance.	erized by laboratory test results that in	ndicate an elevation in the concen	tration of blood sugar. It is usually	an indication of diabetes mellitus	or glucos
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L;	>7.0 mmol/L; life-threatening	Death
туреткатетна	ZOLIN = 3.3 IIIIIO//L	20.0 = 0.0 HIIIIO//L	hospitalization indicated	consequences	Death
Definition: A disorder characte	। erized by laboratory test results that ir	Indicate an elevation in the concen	1	'	I nmetimes
the use of diuretic drugs.	sized by laboratory toot roodito that in	idiodio dii ciovation in the concen	addon or polacolam in the blood, t	docodated with thanley failure of or	Sinoumoo
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23	-	>3.0 - 8.0 mg/dL; >1.23 - 3.30	>8.0 mg/dL; >3.30 mmol/L; life-	Death
•	mmol/L		mmol/L	threatening consequences	
Definition: A disorder characte	erized by laboratory test results that in	ndicate an elevation in the concen	tration of magnesium in the blood		
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L;	>160 mmol/L; life-threatening	Death
			hospitalization indicated	consequences	
Definition: A disorder characte	erized by laboratory test results that in	ndicate an elevation in the concen	tration of sodium in the blood.		
Hypertriglyceridemia	150 mg/dL - 300 mg/dL; 1.71	>300 mg/dL - 500 mg/dL; >3.42	>500 mg/dL - 1000 mg/dL; >5.7	>1000 mg/dL; >11.4 mmol/L;	Death
	mmol/L - 3.42 mmol/L	mmol/L - 5.7 mmol/L	mmol/L - 11.4 mmol/L	life-threatening consequences	
Definition: A disorder characte	erized by laboratory test results that in	ndicate an elevation in the concen	tration of triglyceride concentration	in the blood.	
Hyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L)	-	>ULN - 10 mg/dL (0.59 mmol/L)	>10 mg/dL; >0.59 mmol/L; life-	Death
	without physiologic		with physiologic consequences	threatening consequences	
	consequences				
Definition: A disorder characte	erized by laboratory test results that in	ndicate an elevation in the concen	tration of uric acid.	Ť	
Hypoalbuminemia	<lln -="" 3="" 30="" <lln="" dl;="" g="" l<="" td=""><td><3 - 2 g/dL; <30 - 20 g/L</td><td><2 g/dL; <20 g/L</td><td>Life-threatening consequences;</td><td>Death</td></lln>	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences;	Death
	1	1	1	urgent intervention indicated	1

		Metabolism and nutrition	n disorders		
			Grade		
Adverse Event	1	2	3	4	5
Hypocalcemia	Corrected serum calcium of <lln -="" 2.0<br="" 8.0="" <lln="" dl;="" mg="">mmol/L; lonized calcium <lln -<br="">1.0 mmol/L</lln></lln>	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; lonized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; lonized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences	Death
Definition: A disorder characteriz	ed by laboratory test results that ir	ndicate a low concentration of calc	ium (corrected for albumin) in the	blood.	
Hypoglycemia	<lln -="" 3.0<br="" 55="" <lln="" dl;="" mg="">mmol/L</lln>	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life- threatening consequences; seizures	Death
Definition: A disorder characteriz	ed by laboratory test results that in	ndicate a low concentration of gluc	ose in the blood.		
Hypokalemia	<lln -="" 3.0="" l<="" mmol="" td=""><td><pre><lln -="" 3.0="" l;<br="" mmol="">symptomatic; intervention indicated</lln></pre></td><td><3.0 - 2.5 mmol/L; hospitalization indicated</td><td><2.5 mmol/L; life-threatening consequences</td><td>Death</td></lln>	<pre><lln -="" 3.0="" l;<br="" mmol="">symptomatic; intervention indicated</lln></pre>	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death
Definition: A disorder characteriz	ed by laboratory test results that ir	ndicate a low concentration of pota	assium in the blood.		
Hypomagnesemia	<lln -="" 0.5<br="" 1.2="" <lln="" dl;="" mg="">mmol/L</lln>	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; life-threatening consequences	Death
Definition: A disorder characteriz	ed by laboratory test results that ir	ndicate a low concentration of mag	nesium in the blood.		
Hyponatremia	<lln -="" 130="" l<="" mmol="" td=""><td>-</td><td><130 - 120 mmol/L</td><td><120 mmol/L; life-threatening consequences</td><td>Death</td></lln>	-	<130 - 120 mmol/L	<120 mmol/L; life-threatening consequences	Death
Definition: A disorder characteriz	ed by laboratory test results that ir	ndicate a low concentration of sod	um in the blood.		
Hypophosphatemia	<lln -="" 0.8<br="" 2.5="" <lln="" dl;="" mg="">mmol/L</lln>	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L	<1.0 mg/dL; <0.3 mmol/L; life- threatening consequences	Death
Definition: A disorder characteriz	ed by laboratory test results that in	ndicate a low concentration of pho	sphates in the blood.		
Iron overload	-	Moderate symptoms; intervention not indicated	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by accumulation of iron in the t	issues.			
Obesity	-	BMI 25 - 29.9 kg/m2	BMI 30 - 39.9 kg/m2	BMI >=40 kg/m2	-
Definition: A disorder characteriz	ed by having a high amount of boo	dy fat.			
Tumor lysis syndrome	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by metabolic abnormalities that	result from a spontaneous or the	rapy-related cytolysis of tumor cell	S.	
Metabolism and nutrition disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

	Muscu	loskeletal and connectiv	e tissue disorders		
			Grade		
Adverse Event	1	2	3	4	5
Abdominal soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g. tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by a necrotic process occurring	g in the soft tissues of the abdomir	nal wall.		
Arthralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
	ted by a sensation of marked disco	·	-		1
Arthritis	Mild pain with inflammation, erythema, or joint swelling	Moderate pain associated with signs of inflammation, erythema, or joint swelling; limiting instrumental ADL	Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by inflammation involving a joir	nt.		i	1
Avascular necrosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	red by necrotic changes in the bon nd the destruction of the bone struc		od supply. Most often affecting the	epiphysis of the long bones, the r	ecrotic
Back pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by marked discomfort sensatio	n in the back region.			
Bone pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	red by marked discomfort sensatio	n in the bones.	T	T	1
Buttock pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by marked discomfort sensatio	n in the buttocks.			
Chest wall pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by marked discomfort sensatio	n in the chest wall region.			
Exostosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	-	-
Definition: A disorder characteriz	ed by non-neoplastic overgrowth	of bone.			
Fibrosis deep connective tissue	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration; unable to slide or pinch skin; limiting joint or orifice movement (e.g. mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death
Definition: A disorder characterize	ed by fibrotic degeneration of the	deep connective tissues.			
Flank pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by marked discomfort sensatio	n on the lateral side of the body in	the region below the ribs and abo	ove the hip.	
Generalized muscle weakness	Symptomatic; weakness perceived by patient but not evident on physical exam	Symptomatic; weakness evident on physical exam; weakness limiting instrumental ADL	Weakness limiting self care ADL; disabling	-	-
Definition: A disorder characteriz	red by a reduction in the strength o	of muscles in multiple anatomic sit	es.	T	1
Growth suppression	Reduction in growth velocity by 10 - 29% ideally measured over the period of a year	Reduction in growth velocity by 30 - 49% ideally measured over the period of a year or 0 - 49% reduction in growth from the baseline growth curve	Reduction in growth velocity of >=50% ideally measured over the period of a year	-	-

Grade								
Adverse Event	1	2	3	4	5			
Head soft tissue necrosis	-	Local wound care; medical	Operative debridement or other	Life-threatening consequences;	Death			
		intervention indicated (e.g.,	invasive intervention indicated	urgent intervention indicated				
		dressings or topical	(e.g., tissue reconstruction, flap	3				
		medications)	or grafting)					
Definition: A disorder characterize	ed by a necrotic process occurring	in the soft tissues of the head.	'					
Joint effusion	Asymptomatic; clinical or	Symptomatic; limiting	Severe symptoms; limiting self	-	_			
	diagnostic observations only;	instrumental ADL	care ADL; elective operative					
	intervention not indicated		intervention indicated; disabling					
Definition: A disorder characterize	। ed by excessive fluid in a joint, us।	। ually as a result of ioint inflammati	-		1			
Joint range of motion decreased		>25 - 50% decrease in ROM;	>50% decrease in ROM; limiting	_				
Joint range of motion acordace	motion); decreased ROM	limiting instrumental ADL	self care ADL; disabling					
	limiting athletic activity	innuing modumental / tbL	Self Gare 7 (BE, disabiling					
Definition: A disorder characterize	ed by a decrease in joint flexibility	of any joint	I		1			
Joint range of motion decreased	Mild restriction of rotation or	Rotation <60 degrees to right or	Ankylosed/fused over multiple					
cervical spine			segments with no C-spine		-			
oor riodi apinit	noxion between ou - 70 degrees	non, sou dogrees of flexion	rotation					
Definition: A disorder characterize	ed by a decrease in flevibility of a	l cenvical spine joint	J		I			
	ed by a decrease in flexibility of a		cEOO/ lumbar ari fi					
Joint range of motion decreased	Stiffness; difficulty bending to	Pain with range of motion	<50% lumbar spine flexion;	-	-			
lumbar spine	the floor to pick up a very light	(ROM) in lumbar spine; requires	associated with symptoms of					
	object but able to do athletic	a reaching aid to pick up a very	ankylosis or fused over multiple					
	activity	light object from the floor	segments with no L-spine					
			flexion (e.g., unable to reach to					
			floor to pick up a very light					
			object)					
Definition: A disorder characterize	ed by a decrease in flexibility of a	lumbar spine joint.	T					
Kyphosis	Asymptomatic; clinical or	Moderate accentuation; limiting	Severe accentuation; operative	-	-			
	diagnostic observations only;	instrumental ADL	intervention indicated; limiting					
	intervention not indicated		self care ADL					
Definition: A disorder characterize	ed by an abnormal increase in the	curvature of the thoracic portion of	of the spine.					
Lordosis	Asymptomatic; clinical or	Moderate accentuation; limiting	Severe accentuation; operative	-	-			
	diagnostic observations only;	instrumental ADL	intervention indicated; limiting					
	intervention not indicated		self care ADL					
Definition: A disorder characterize	ed by an abnormal increase in the	curvature of the lumbar portion of	f the spine.		•			
Muscle weakness left-sided	Symptomatic; perceived by	Symptomatic; evident on	Limiting self care ADL; disabling	_	_			
	patient but not evident on	physical exam; limiting						
	physical exam	instrumental ADL						
Definition: A disorder characterize	ed by a reduction in the strength o	ı	e bodv.	l	1			
Muscle weakness lower limb	Symptomatic; perceived by	Symptomatic; evident on	Limiting self care ADL; disabling	_				
Widdle Weakiness lower limb	patient but not evident on	physical exam; limiting	Eliming Sch Care ADE, disabiling	_				
	physical exam	instrumental ADL						
Definition: A disorder characteriz	ed by a reduction in the strength o	ı	I		ı			
			Limiting colf core ADL: dis-11"					
Muscle weakness right-sided	Symptomatic; perceived by	Symptomatic; evident on	Limiting self care ADL; disabling	· -	-			
	patient but not evident on	physical exam; limiting						
- • · · · · · · · · · · · · · · · · · ·	physical exam	instrumental ADL	1		I			
Definition: A disorder characterize	ed by a reduction in the strength o		the body.		1			
Muscle weakness trunk	Symptomatic; perceived by	Symptomatic; evident on	Limiting self care ADL; disabling	-	-			
	patient but not evident on	physical exam; limiting						
	physical exam	instrumental ADL						
Definition: A disorder characterize	ed by a reduction in the strength o	f the trunk muscles.						
	ed by a reduction in the strength o	f the trunk muscles. Symptomatic; evident on	Limiting self care ADL; disabling	-	-			
		Symptomatic; evident on	Limiting self care ADL; disabling	-	-			
Definition: A disorder characterize Muscle weakness upper limb	Symptomatic; perceived by		Limiting self care ADL; disabling	-	-			

Musculoskeletal and connective tissue disorders								
	Grade 1 2 3 4 5							
Adverse Event	1			4	5			
Musculoskeletal deformity	Cosmetically and functionally insignificant hypoplasia	Deformity, hypoplasia, or asymmetry able to be remediated by prosthesis (e.g., shoe insert) or covered by clothing	Significant deformity, hypoplasia, or asymmetry, unable to be remediated by prosthesis or covered by clothing; disabling	-	-			
Definition: A disorder character	ized by of a malformation of the mu	sculoskeletal system.						
Myalgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder character	ized by marked discomfort sensatio	n originating from a muscle or gro	up of muscles.					
Myositis	Mild pain	Moderate pain associated with weakness; pain limiting instrumental ADL	Pain associated with severe weakness; limiting self care ADL	-	-			
Definition: A disorder character	ized by inflammation involving the s	keletal muscles.						
Neck pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder character	ized by marked discomfort sensatio	n in the neck area.	T	T				
Neck soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder character	ized by a necrotic process occurring	in the soft tissues of the neck.						
Osteonecrosis of jaw	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (e.g., topical agents); limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder character	ized by a necrotic process occurring	in the bone of the mandible.						
Osteoporosis	Radiologic evidence of osteoporosis or Bone Mineral Density (BMD) t-score -1 to -2.5 (osteopenia); no loss of height or intervention indicated	BMD t-score <-2.5; loss of height <2 cm; anti-osteoporotic therapy indicated; limiting instrumental ADL	Loss of height >=2 cm; hospitalization indicated; limiting self care ADL	-	-			
Definition: A disorder charactericomposition), resulting in increase	ized by reduced bone mass, with a ased fracture incidence.	decrease in cortical thickness and	l in the number and size of the trab	peculae of cancellous bone (but no	ormal chemi			
Pain in extremity	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder character	ized by marked discomfort sensatio	n in the upper or lower extremities	S					
Pelvic soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death			
Scoliosis	<20 degrees; clinically		>45 dogrado: acapular					
SCOIIOSIS	undetectable	>20 - 45 degrees; visible by forward flexion; limiting instrumental ADL	>45 degrees; scapular prominence in forward flexion; operative intervention indicated; limiting self care ADL; disabling		-			
Definition: A disorder character	ized by a malformed, lateral curvatu	re of the spine.	T	ı				
Soft tissue necrosis lower limb	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder character	ized by a necrotic process occurring	g in the soft tissues of the lower ex	ctremity.	<u> </u>				
Soft tissue necrosis upper limb	-	Local wound care; medical intervention indicated (e.g., dressings or topical	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap	Life-threatening consequences; urgent intervention indicated	Death			

	Muscu	loskeletal and connectiv	e tissue disorders				
Grade							
Adverse Event	1	2	3	4	5		
Superficial soft tissue fibrosis	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration; unable to slide or pinch skin; limiting joint or orifice movement (e.g., mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death		
Definition: A disorder characterize	ed by fibrotic degeneration of the s	superficial soft tissues.					
Trismus	Decreased ROM (range of motion) without impaired eating	Decreased ROM requiring small bites, soft foods or purees	Decreased ROM with inability to adequately aliment or hydrate orally	-	-		
Definition: A disorder characterize	ed by lack of ability to open the mo	outh fully due to a decrease in the	range of motion of the muscles of	mastication.			
Unequal limb length	Mild length discrepancy <2 cm	Moderate length discrepancy 2 - 5 cm; shoe lift indicated; limiting instrumental ADL	, ,	-	-		
Definition: A disorder characterize	ed by of a discrepancy between th	e lengths of the lower or upper ex	tremities.				
Musculoskeletal and connective tissue disorder - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death		

	Neoplasms benig	n, malignant and unspec	cified (incl cysts and poly	yps)				
		Grade						
Adverse Event	1	2	3	4	5			
Leukemia secondary to oncology chemotherapy	-	-	-	Present	Death			
Definition: A disorder characterize	ed by leukemia arising as a result	of the mutagenic effect of chemot	herapy agents.					
Myelodysplastic syndrome	-	-	-	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characterize	ed by insufficiently healthy hemata	poietic cell production by the bone	e marrow.					
Treatment related secondary malignancy	-	-	Non life-threatening secondary malignancy	Acute life-threatening secondary malignancy; blast crisis in leukemia	Death			
Definition: A disorder characterize	ed by development of a malignanc	by most probably as a result of trea	atment for a previously existing ma	alignancy.				
Tumor pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characterize	ed by marked discomfort from a ne	eoplasm that may be pressing on	a nerve, blocking blood vessels, ir	nflamed or fractured from metastas	sis.			
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death			

Nervous system disorders							
		T	Grade	T	1		
Adverse Event	1	2	3	4	5		
Abducens nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-		
Definition: A disorder characteri	ized by involvement of the abducen	s nerve (sixth cranial nerve).	<u> </u>				
Accessory nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-		
Definition: A disorder characteri	ized by involvement of the accessor	ry nerve (eleventh cranial nerve).	.	T			
Acoustic nerve disorder NOS	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-		
Definition: A disorder characteri	ized by involvement of the acoustic	nerve (eighth cranial nerve).	T	T	1		
Akathisia	Mild restlessness or increased motor activity	Moderate restlessness or increased motor activity; limiting instrumental ADL	Severe restlessness or increased motor activity; limiting self care ADL	-	-		
Definition: A disorder characteri	ized by an uncomfortable feeling of	inner restlessness and inability to	stay still; this is a side effect of so	me psychotropic drugs.			
Amnesia	Mild; transient memory loss	Moderate; short term memory loss; limiting instrumental ADL	Severe; long term memory loss; limiting self care ADL	-	-		
	ized by systematic and extensive lo	ss or memory.	V. 1				
Aphonia	-	-	Voicelessness; unable to speak	1	-		
	ized by the inability to speak. It may			1	l		
Arachnoiditis	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death		
	ized by inflammation of the arachno						
Ataxia	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; mechanical assistance indicated	-	-		
Definition: A disorder characteri	ized by lack of coordination of musc	cle movements resulting in the imp	airment or inability to perform volu	intary activities.			
Brachial plexopathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-		
Definition: A disorder characteri	ized by regional paresthesia of the l	brachial plexus, marked discomfor	t and muscle weakness, and limite	ed movement in the arm or hand.			
Central nervous system necrosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; corticosteroids indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteri	ized by a necrotic process occurring	g in the brain and/or spinal cord.					
Cerebrospinal fluid leakage	Post-craniotomy: asymptomatic; Post-lumbar puncture: transient headache; postural care indicated	Post-craniotomy: moderate symptoms; medical intervention indicated; Post-lumbar puncture: persistent moderate symptoms; blood patch indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteri	ized by loss of cerebrospinal fluid in	to the surrounding tissues.					
Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	-	-		
Definition: A disorder characteri	ized by a conspicuous change in co	gnitive function.					
Concentration impairment	Mild inattention or decreased level of concentration	Moderate impairment in attention or decreased level of concentration; limiting instrumental ADL	Severe impairment in attention or decreased level of concentration; limiting self care ADL	-	-		

Nervous system disorders								
Grade								
Adverse Event	1	2	3	4	5			
Depressed level of consciousness	Decreased level of alertness	Sedation; slow response to stimuli; limiting instrumental ADL	Difficult to arouse	Life-threatening consequences	Death			
Definition: A disorder characte	erized by a decrease in ability to perc	eive and respond.	T	T				
Dizziness	Mild unsteadiness or sensation of movement	Moderate unsteadiness or sensation of movement; limiting instrumental ADL	Severe unsteadiness or sensation of movement; limiting self care ADL	-	-			
Definition: A disorder characte	erized by a disturbing sensation of lig	htheadedness, unsteadiness, gidd	liness, spinning or rocking.		,			
Dysarthria	Mild slurred speech	Moderate impairment of articulation or slurred speech	Severe impairment of articulation or slurred speech	-	-			
Definition: A disorder characte	erized by slow and slurred speech res	sulting from an inability to coordina	ate the muscles used in speech.	1	1			
Dysesthesia	Mild sensory alteration	Moderate sensory alteration; limiting instrumental ADL	Severe sensory alteration; limiting self care ADL	-	-			
Definition: A disorder characte	erized by distortion of sensory percep	tion, resulting in an abnormal and	unpleasant sensation.	1	1			
Dysgeusia	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	-	-	-			
Definition: A disorder characte	erized by abnormal sensual experien	ce with the taste of foodstuffs; it ca	an be related to a decrease in the	sense of smell.				
Dysphasia	Awareness of receptive or expressive characteristics; not impairing ability to communicate	Moderate receptive or expressive characteristics; impairing ability to communicate spontaneously	Severe receptive or expressive characteristics; impairing ability to read, write or communicate intelligibly	-	-			
Definition: A disorder characte	erized by impairment of verbal comm	unication skills, often resulting fron	n brain damage.					
Edema cerebral	-	-	-	Life-threatening consequences; urgent intervention indicated	-			
Definition: A disorder character	erized by swelling due to an excessiv	e accumulation of fluid in the brain).	ı				
Encephalopathy	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characte	erized by a pathologic process involvi	ing the brain.	1	1	1			
Extrapyramidal disorder	Mild involuntary movements	Moderate involuntary movements; limiting instrumental ADL	Severe involuntary movements or torticollis; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characte	erized by abnormal, repetitive, involui	ntary muscle movements, frenzied	speech and extreme restlessness	· 3.				
Facial muscle weakness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-			
Definition: A disorder characte	erized by a reduction in the strength o	of the facial muscles.						
Facial nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-			
Definition: A disorder characte	erized by involvement of the facial ne	rve (seventh cranial nerve).						
Glossopharyngeal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characte	erized by involvement of the glossoph	naryngeal nerve (ninth cranial nerv	re).					
Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characte	erized by a sensation of marked disco	omfort in various parts of the head	, not confined to the area of distrib	ution of any nerve.				
Hydrocephalus	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; intervention not indicated	Severe symptoms or neurological deficit; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characte	erized by an abnormal increase of ce	rebrospinal fluid in the ventricles o	f the brain.					
Hypersomnia	Mild increased need for sleep	Moderate increased need for sleep	Severe increased need for sleep	-	-			
Definition: A disorder character	erized by characterized by excessive	sleepiness during the daytime	•	•	•			

Nervous system disorders Grade							
Adverse Event	1	2	3	4	5		
Hypoglossal nerve disorder	Asymptomatic; clinical or	Moderate symptoms; limiting	Severe symptoms; limiting self		-		
,,pegiocea no ve alcondo.	diagnostic observations only; intervention not indicated	instrumental ADL	care ADL				
Definition: A disorder characteri	zed by involvement of the hypoglos	sal nerve (twelfth cranial nerve).	I	ı	ı		
Intracranial hemorrhage	Asymptomatic; clinical or	Moderate symptoms; medical	Ventriculostomy, ICP	Life-threatening consequences;	Death		
	diagnostic observations only; intervention not indicated	intervention indicated	monitoring, intraventricular thrombolysis, or operative intervention indicated	urgent intervention indicated			
Definition: A disorder characteri	zed by bleeding from the cranium.						
schemia cerebrovascular	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	-	-	-		
Definition: A disorder characteri damage.	zed by a decrease or absence of bl	ood supply to the brain caused by	obstruction (thrombosis or embol	lism) of an artery resulting in neuro	ological		
Vth nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-		
Definition: A disorder characteri	zed by involvement of the trochlear	nerve (fourth cranial nerve).		1			
Lethargy	Mild symptoms; reduced alertness and awareness	Moderate symptoms; limiting instrumental ADL	-	-	-		
Definition: A disorder characteri	zed by a decrease in consciousnes	s characterized by mental and ph	ysical inertness.				
Leukoencephalopathy	Asymptomatic; small focal T2/FLAIR hyperintensities; involving periventricular white matter or <1/3 of susceptible areas of cerebrum +/- mild increase in subarachnoid space (SAS) and/or mild ventriculomegaly	Moderate symptoms; focal T2/FLAIR hyperintensities, involving periventricular white matter extending into centrum semiovale or involving 1/3 to 2/3 of susceptible areas of cerebrum +/- moderate increase in SAS and/or moderate ventriculomegaly	Severe symptoms; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving 2/3 or more of susceptible areas of cerebrum +/- moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Life-threatening consequences; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving most of susceptible areas of cerebrum +/- moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Death		
Definition: A disorder characteri	zed by diffuse reactive astrocytosis	with multiple areas of necrotic for	i without inflammation.	•	'		
Memory impairment	Mild memory impairment	Moderate memory impairment; limiting instrumental ADL	Severe memory impairment; limiting self care ADL	-	-		
Definition: A disorder characteri	ਾ zed by a deterioration in memory fu	-		1	ı		
Meningismus	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteri	zed by neck stiffness, headache, a	nd photophobia resulting from irrita	1		1		
Movements involuntary	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-		
Definition: A disorder characteri	zed by uncontrolled and purposeles	ss movements.			1		
Myelitis	Asymptomatic; mild signs (e.g., Babinski's reflex or Lhermitte's sign)	Moderate weakness or sensory loss; limiting instrumental ADL	Severe weakness or sensory loss; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteri	zed by inflammation involving the s	pinal cord. Symptoms include wea	akness, paresthesia, sensory loss. T	, marked discomfort and incontine	nce.		
Neuralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-		
	zed by intense painful sensation ald		l.		1		
Nystagmus	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-		
Definition: A disorder characteri	zed by involuntary movements of th	ne eyeballs.	T	I	1		
Oculomotor nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-		
Definition: A disorder characteri	zed by involvement of the oculomo	tor nerve (third cranial nerve).	T	1			
Olfactory nerve disorder	-	Moderate symptoms; limiting	Severe symptoms; limiting self	-	-		

		Nervous system dis	orders		
		·	Grade		
Adverse Event	1	2	3	4	5
Paresthesia	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characteriz are experienced in the absence of	•	ensory neurons resulting in abnor	mal cutaneous sensations of tingli	ng, numbness, pressure, cold, and	warmth that
Peripheral motor neuropathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; assistive device indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by inflammation or degeneration	on of the peripheral motor nerves.			
Peripheral sensory neuropathy	Asymptomatic; loss of deep tendon reflexes or paresthesia	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
	1	on of the peripheral sensory nerve			
Phantom pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by marked discomfort related to		ed from or is not physically part of	the body.	
Presyncope	-	Present (e.g., near fainting)	-	-	-
Definition: A disorder characteriz	ed by an episode of lightheadedne	ess and dizziness which may prec	ede an episode of syncope.	T	I
Pyramidal tract syndrome	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
	ed by dysfunction of the corticospi nd a decrease in fine motor coord		l cord. Symptoms include an incre	ease in the muscle tone in the lowe	er extremities,
Radiculitis	Mild symptoms	Moderate symptoms; limiting instrumental ADL; medical intervention indicated	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz connecting nerve root.	ed by inflammation involving a ne	rve root. Patients experience mark	ed discomfort radiating along a ne	erve path because of spinal pressu	re on the
Recurrent laryngeal nerve palsy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	Severe symptoms; medical intervention indicated (e.g., thyroplasty, vocal cord injection)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by paralysis of the recurrent la	ryngeal nerve.			
Reversible posterior leukoencephalopathy syndrome	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; abnormal imaging studies; limiting instrumental ADL	Severe symptoms; very abnormal imaging studies; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
	-	=		indings of posterior leukoencepha s an acute or subacute reversible	
Seizure	Brief partial seizure; no loss of consciousness	Brief generalized seizure	Multiple seizures despite medical intervention	Life-threatening; prolonged repetitive seizures	Death
Definition: A disorder characteriz	ed by a sudden, involuntary skele	tal muscular contractions of cereb	ral or brain stem origin.	T	
Sinus pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by marked discomfort in the fac	ce, between the eyes, or upper tee	eth originating from the sinuses.	T	
Somnolence	Mild but more than usual drowsiness or sleepiness	Moderate sedation; limiting instrumental ADL	Obtundation or stupor	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by characterized by excessive	sleepiness and drowsiness.		1	
Spasticity	Mild or slight increase in muscle tone	Moderate increase in muscle tone and increase in resistance through range of motion	Severe increase in muscle tone and increase in resistance through range of motion	Life-threatening; unable to move active or passive range of motion	Death
Definition: A disorder characteriz disturbances.	ed by increased involuntary musc	le tone that affects the regions inte	erfering with voluntary movement.	It results in gait, movement, and s	peech
Stroke	Asymptomatic or mild neurologic deficit; radiographic findings only	Moderate neurologic deficit	Severe neurologic deficit	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by a sudden loss of sensory fu	nction due to an intracranial vascu	ılar event.	1	ı
Syncope Definition: A disorder characteriz	- ed by spontaneous loss of conscie	- cusness caused by insufficient blo	Fainting; orthostatic collapse od supply to the brain.	-	-

		Nervous system dis	orders						
	Grade								
Adverse Event	1	2	3	4	5				
Transient ischemic attacks	Mild neurologic deficit with or without imaging confirmation	Moderate neurologic deficit with or without imaging confirmation	-	-	-				
Definition: A disorder characteriz	ed by a brief attack (less than 24 h	nours) of cerebral dysfunction of va	ascular origin, with no persistent n	eurological deficit.					
Tremor	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-				
Definition: A disorder characteriz	ed by the uncontrolled shaking mo	vement of the whole body or indiv	ridual parts.						
Trigeminal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-				
Definition: A disorder characteriz	ed by involvement of the trigemina	l nerve (fifth cranial nerve).							
Vagus nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death				
Definition: A disorder characteriz	ed by involvement of the vagus ne	rve (tenth cranial nerve).							
Vasovagal reaction	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death				
Definition: A disorder characteriz increase in the stimulation of the	ed by a sudden drop of the blood progression vagus nerve.	oressure, bradycardia, and periph	eral vasodilation that may lead to	loss of consciousness. It results fr	om an				
Nervous system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death				

. 1	2	Grade 3	4	
1	2	3	4	
			-7	5
	-	-	-	Fetal loss at any gestational age
I by death in utero; failure of the p	product of conception to show evi-	dence of respiration, heartbeat, or	definite movement of a voluntary	muscle after
possibility of resuscitation.				
-	<10% percentile of weight for gestational age	<5% percentile of weight for gestational age	<1% percentile of weight for gestational age	-
by inhibition of fetal growth resu	lting in the inability of the fetus to	achieve its potential weight.		
1	*	Delivery of a liveborn infant at 24 to 28 weeks gestation	Delivery of a liveborn infant at 24 weeks of gestation or less	-
l by delivery of a viable infant bef	ore the normal end of gestation.	Typically, viability is achievable be	tween the twentieth and thirty-sev	enth week of
-	-	Unintended pregnancy	-	-
by an unexpected pregnancy at	the time of conception.	•	•	·
ymptoms; clinical or diagnostic	intervention indicated; limiting	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated;	Life-threatening consequences; urgent intervention indicated	Death
	by inhibition of fetal growth resultivery of a liveborn infant at 14 to 37 weeks gestation by delivery of a viable infant before an unexpected pregnancy at symptomatic or mild mptoms; clinical or diagnostic isservations only; intervention	symptoms; clinical or diagnostic uservations only; intervention only; intervention only; intervention in sessibility of resuscitation. 10% percentile of weight for gestational age by inhibition of fetal growth resulting in the inability of the fetus to Delivery of a liveborn infant at 28 to 34 weeks gestation by delivery of a viable infant before the normal end of gestation by an unexpected pregnancy at the time of conception. Moderate, local or noninvasive intervention indicated; limiting instrumental ADL	Comparison of the content of the c	<10% percentile of weight for gestational age <5% percentile of weight for gestational age <1% percentile of weight for gestation and in gestation in strument at <1% percentile of weight for gestation age <1% percentile of weight for gestational age <1% percentile of sestation achieved <1% percentile of sestation <1% percen

		Psychiatric disor	ders		
			Grade		
Adverse Event	1	2	3	4	5
Agitation	Mild mood alteration	Moderate mood alteration	Severe agitation; hospitalization not indicated	Life-threatening consequences; urgent intervention indicated	Death
	erized by a state of restlessness asso		irritability and tension.		
Anorgasmia	Inability to achieve orgasm not adversely affecting relationship	Inability to achieve orgasm adversely affecting relationship	-	-	-
Definition: A disorder characte	erized by an inability to achieve orgas				
Anxiety	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization not indicated	Life-threatening; hospitalization indicated	Death
Definition: A disorder characte stimulus.	erized by apprehension of danger and	d dread accompanied by restlessn	ess, tension, tachycardia, and dys	pnea unattached to a clearly ident	tifiable
Confusion	Mild disorientation	Moderate disorientation; limiting instrumental ADL	Severe disorientation; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	erized by a lack of clear and orderly the	nought and behavior.			
Delayed orgasm	Delay in achieving orgasm not adversely affecting relationship	Delay in achieving orgasm adversely affecting relationship	-	-	-
	erized by sexual dysfunction characte		<u> </u>	I	I
Delirium	Mild acute confusional state	Moderate and acute confusional state; limiting instrumental ADL	Severe and acute confusional state; limiting self care ADL; hospitalization indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characte reversible condition.	erized by the acute and sudden devel	opment of confusion, illusions, mo	vement changes, inattentiveness,	agitation, and hallucinations. Usu	ally, it is a
Delusions	-	Moderate delusional symptoms	Severe delusional symptoms; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characte	erized by false personal beliefs held c	contrary to reality, despite contradi	ctory evidence and common sense	e.	•
Depression	Mild depressive symptoms	Moderate depressive symptoms; limiting instrumental ADL	Severe depressive symptoms; limiting self care ADL; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characte	erized by melancholic feelings of grief	f or unhappiness.	'	'	•
Euphoria	Mild mood elevation	Moderate mood elevation	Severe mood elevation (e.g., hypomania)	-	-
Definition: A disorder characte	erized by an exaggerated feeling of w	ell-being which is disproportionate	to events and stimuli.		
Hallucinations	Mild hallucinations (e.g., perceptual distortions)	Moderate hallucinations	Severe hallucinations; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characte	erized by a false sensory perception i	n the absence of an external stime	ılus.		
Insomnia	Mild difficulty falling asleep, staying asleep or waking up early	Moderate difficulty falling asleep, staying asleep or waking up early	Severe difficulty in falling asleep, staying asleep or waking up early	-	-
Definition: A disorder characte	erized by difficulty in falling asleep an	d/or remaining asleep.	1	1	
Libido decreased	Decrease in sexual interest not adversely affecting relationship	Decrease in sexual interest adversely affecting relationship	-	-	-
Definition: A disorder characte	erized by a decrease in sexual desire	T	T	T	
Libido increased	Mild increase in sexual interest not adversely affecting relationship	Moderate increase in sexual interest adversely affecting relationship	Severe increase in sexual interest leading to dangerous behavior	-	-
Definition: A disorder characte	erized by an increase in sexual desire	e			
Mania	Mild manic symptoms (e.g., elevated mood, rapid thoughts, rapid speech, decreased need for sleep)	Moderate manic symptoms (e.g., relationship and work difficulties; poor hygiene)	Severe manic symptoms (e.g., hypomania; major sexual or financial indiscretions); hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characte	erized by excitement of psychotic property	portions manifested by mental and	l physical hyperactivity, disorganiz	ation of behavior and elevation of	mood.
Personality change	Mild personality change	Moderate personality change	Severe personality change; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death

		Psychiatric disord	ders					
	Grade							
Adverse Event	1	2	3	4	5			
Definition: A disorder characterize	ed by a conspicuous change in a p	person's behavior and thinking.						
Psychosis	Mild psychotic symptoms	Moderate psychotic symptoms (e.g., disorganized speech; impaired reality testing)	Severe psychotic symptoms (e.g., paranoid; extreme disorganization); hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death			
Definition: A disorder characterize tumor.	ed by personality change, impaired	d functioning, and loss of touch wi	th reality. It may be a manifestatio	n of schizophrenia, bipolar disorde	er or brain			
Restlessness	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-			
Definition: A disorder characterize	ed by an inability to rest, relax or b	e still.						
Suicidal ideation	Increased thoughts of death but no wish to kill oneself	Suicidal ideation with no specific plan or intent	Specific plan to commit suicide without serious intent to die which may not require hospitalization	Specific plan to commit suicide with serious intent to die which requires hospitalization	-			
Definition: A disorder characterize	ed by thoughts of taking one's owr	n life.						
Suicide attempt	-	-	Suicide attempt or gesture without intent to die which may not require hospitalization	Suicide attempt with intent to die which requires hospitalization	Death			
Definition: A disorder characterize	ed by self-inflicted harm in an atte	mpt to end one's own life.						
Psychiatric disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; disabling; limiting self care ADL	Life-threatening consequences; hospitalization or urgent intervention indicated	Death			

causes (ureteral or bladder outflo Bladder perforation	t Creatinine level increase of >0.3 mg/dL; creatinine 1.5 - 2.0 x above baseline ed by the acute loss of renal function obstruction).	baseline	Grade 3 Creatinine >3 x baseline or >4.0 mg/dL; hospitalization indicated s pre-renal (low blood flow into kidi	4 Life-threatening consequences; dialysis indicated	5 Death
Acute kidney injury Definition: A disorder characterize causes (ureteral or bladder outflo	Creatinine level increase of >0.3 mg/dL; creatinine 1.5 - 2.0 x above baseline ed by the acute loss of renal functi	Creatinine 2 - 3 x above baseline on and is traditionally classified as	Creatinine >3 x baseline or >4.0 mg/dL; hospitalization indicated	Life-threatening consequences;	
Definition: A disorder characterize causes (ureteral or bladder outflo Bladder perforation	mg/dL; creatinine 1.5 - 2.0 x above baseline ed by the acute loss of renal functi	baseline on and is traditionally classified as	mg/dL; hospitalization indicated		Death
causes (ureteral or bladder outflo	•	-		 nev)renal (kidnev damage) and r	ost-renal
	-	Extraperitoneal perforation,		noy), ronal (Manoy damago) and p	oot ronar
		indwelling catheter indicated	Intraperitoneal perforation; elective radiologic, endoscopic or operative intervention indicated	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
Definition: A disorder characterize	ed by a rupture in the bladder wall.			<u> </u>	1
Bladder spasm	Intervention not indicated	Antispasmodics indicated	Hospitalization indicated	-	-
Definition: A disorder characterize	ed by a sudden and involuntary co	ntraction of the bladder wall.			
Chronic kidney disease	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <lln -="" 60<br="">ml/min/1.73 m2 or proteinuria 2+ present; urine protein/creatinine >0.5</lln>	eGFR or CrCl 59 - 30 ml/min/1.73 m2	eGFR or CrCl 29 - 15 ml/min/1.73 m2	eGFR or CrCl <15 ml/min/1.73 m2; dialysis or renal transplant indicated	Death
Definition: A disorder characterize	ed by gradual and usually perman	ent loss of kidney function resulting	g in renal failure.		
Cystitis noninfective	Microscopic hematuria; minimal increase in frequency, urgency, dysuria, or nocturia; new onset of incontinence	Moderate hematuria; moderate increase in frequency, urgency, dysuria, nocturia or incontinence; urinary catheter placement or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characterize	ed by inflammation of the bladder	which is not caused by an infectio	n of the urinary tract.	•	•
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated; limiting self care ADL	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characterize	ed by laboratory test results that in	dicate blood in the urine.		.	
Hemoglobinuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characterize	ed by laboratory test results that in	dicate the presence of free hemo	globin in the urine.		
Proteinuria	1+ proteinuria; urinary protein <1.0 g/24 hrs	Adults: 2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Pediatric: urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Adults: urinary protein >=3.5 g/24 hrs; Pediatric: urine P/C >1.9	-	-
Definition: A disorder characterize	ed by laboratory test results that in	dicate the presence of excessive	protein in the urine. It is predomina	antly albumin, but also globulin.	
Renal calculi	Asymptomatic or mild symptoms; occasional use of nonprescription analgesics indicated	Symptomatic; oral antiemetics indicated; around the clock nonprescription analgesics or any oral narcotic analgesics indicated	Hospitalization indicated; IV intervention (e.g., analgesics, antiemetics); elective endoscopic or radiologic intervention indicated	Life-threatening consequences; urgent radiologic, endoscopic or operative intervention indicated	Death
Definition: A disorder characterize	ed by the formation of crystals in the	ne pelvis of the kidney.	T	Γ	
Renal colic	Mild pain not interfering with activity; nonprescription medication indicated	Moderate pain; limiting instrumental ADL; prescription medication indicated	Hospitalization indicated; limiting self care ADL	-	-

	Renal and urinary disorders							
			Grade					
Adverse Event	1	2	3	4	5			
Renal hemorrhage	Mild symptoms; intervention not indicated	Analgesics and hematocrit monitoring indicated	Transfusion, radiation, or hospitalization indicated; elective radiologic, endoscopic or operative intervention indicated	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death			
Definition: A disorder character	rized by bleeding from the kidney.							
Urinary fistula	-	Noninvasive intervention indicated; urinary or suprapubic catheter placement indicated	Limiting self care ADL; elective radiologic, endoscopic or operative intervention indicated; permanent urinary diversion indicated	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death			
Definition: A disorder character	rized by an abnormal communication	between any part of the urinary s	system and another organ or anato	omic site.				
Urinary frequency	Present	Limiting instrumental ADL; medical management indicated	-	-	-			
Definition: A disorder character	rized by urination at short intervals.	T	T	T	_			
Urinary incontinence	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous; pads indicated; limiting instrumental ADL	Intervention indicated (e.g., clamp, collagen injections); operative intervention indicated; limiting self care ADL	-	-			
Definition: A disorder character	rized by inability to control the flow o	f urine from the bladder.						
Urinary retention	Urinary, suprapubic or intermittent catheter placement not indicated; able to void with some residual	Placement of urinary, suprapubic or intermittent catheter placement indicated; medication indicated	Elective operative or radiologic intervention indicated; substantial loss of affected kidney function or mass	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death			
Definition: A disorder character	rized by accumulation of urine within	the bladder because of the inabil	ity to urinate.					
Urinary tract obstruction	Asymptomatic; clinical or diagnostic observations only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; urethral dilation, urinary or suprapubic catheter indicated	Symptomatic and altered organ function (e.g., hydronephrosis, or renal dysfunction); elective radiologic, endoscopic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder character	rized by blockage of the normal flow	of contents of the urinary tract.	T	T				
Urinary tract pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder character	rized by a sensation of marked disco	omfort in the urinary tract.	1	1				
Jrinary urgency	Present	Limiting instrumental ADL; medical management indicated	-	-	-			
Definition: A disorder character	rized by a sudden compelling urge to	o urinate.	1	1				
Jrine discoloration	Present	-	-	-	-			
Definition: A disorder character	rized by a change in the color of the	urine.						
Renal and urinary disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate, local or noninvasive intervention indicated; limiting instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death			

	Rep	productive system and b	reast disorders		
			Grade		
Adverse Event	1	2	3	4	5
Azoospermia	-	-	Absence of sperm in ejaculate	-	-
Definition: A disorder characte	rized by laboratory test results that ir	ndicate complete absence of speri	matozoa in the semen.		
Breast atrophy	Minimal asymmetry; minimal	Moderate asymmetry; moderate	Asymmetry >1/3 of breast	-	-
	atrophy	atrophy	volume; severe atrophy		
Definition: A disorder characte	rized by underdevelopment of the br	east.			
Breast pain	Mild pain	Moderate pain; limiting	Severe pain; limiting self care	-	-
		instrumental ADL	ADL		
Definition: A disorder characte	rized by marked discomfort sensatio	n in the breast region.			
Dysmenorrhea	Mild symptoms; intervention not	Moderate symptoms; limiting	Severe symptoms; limiting self	-	-
	indicated	instrumental ADL	care ADL		
Definition: A disorder characte	rized by abnormally painful abdomin	al cramps during menses.			
Dyspareunia	Mild discomfort or pain	Moderate discomfort or pain	Severe discomfort or pain	-	_
•	associated with vaginal	associated with vaginal	associated with vaginal		
	penetration; discomfort relieved	penetration; discomfort or pain	penetration; discomfort or pain		
	with use of vaginal lubricants or	partially relieved with use of	unrelieved by vaginal lubricants		
	estrogen	vaginal lubricants or estrogen	or estrogen		
Definition: A disorder characte	rized by painful or difficult coitus.	T	1	1	
Ejaculation disorder	Diminished ejaculation	Anejaculation or retrograde	-	-	-
		ejaculation			
Definition: A disorder characte	rized by problems related to ejaculat	ion. This category includes prema	ture, delayed, retrograde and pair	nful ejaculation.	
Erectile dysfunction	Decrease in erectile function	Decrease in erectile function	Decrease in erectile function	-	-
	(frequency or rigidity of	(frequency/rigidity of erections),	(frequency/rigidity of erections)		
	erections) but intervention not	erectile intervention indicated,	but erectile intervention not		
	indicated (e.g., medication or	(e.g., medication or mechanical	helpful (e.g., medication or		
	use of mechanical device, penile pump)	devices such as penile pump)	mechanical devices such as penile pump); placement of a		
	perme pump)		permanent penile prosthesis		
			indicated (not previously		
			present)		
Definition: A disorder characte	rized by the persistent or recurrent ir	nability to achieve or to maintain a	n erection during sexual activity.	•	•
Fallopian tube obstruction	Diagnostic observations only;	Mild symptoms; elective	Severe symptoms; elective	_	_
	intervention not indicated	intervention indicated	operative intervention indicated		
Definition: A disorder characte	rized by blockage of the normal flow	of the contents in the fallopian tul	De.	1	'
Fallopian tube stenosis	Asymptomatic clinical or	Symptomatic and intervention	Severe symptoms; elective	Life-threatening consequences;	Death
allopian tube steriosis	diagnostic observations only;	not indicated	operative intervention indicated	urgent operative intervention	Death
	intervention not indicated			indicated (e.g., organ resection)	
Definition: A disorder characte	rized by a narrowing of the fallopian	tube lumen.	'		'
Female genital tract fistula	Asymptomatic clinical or	Symptomatic and intervention	Severe symptoms; elective	Life-threatening consequences;	Death
ornalo gorniai traot notala	diagnostic observations only;	not indicated	operative intervention indicated	urgent intervention indicated	Bouti
	intervention not indicated		'		
Definition: A disorder characte	rized by an abnormal communication	n between a female reproductive s	vstem organ and another organ o	r anatomic site.	'
Feminization acquired	Mild symptoms; intervention not	1]_		I_
ommzadon doganod	indicated	intervention indicated			
Definition: A disorder characte	rized by the development of seconda	ı	ales due to extrinsic factors.	1	1
Genital edema	Mild swelling or obscuration of	Readily apparent obscuration of	Lymphorrhea; gross deviation	_	I -
Co.mai Gaoilla	anatomic architecture on close	anatomic architecture;	from normal anatomic contour;		
	inspection	obliteration of skin folds; readily	limiting self care ADL		
		apparent deviation from normal			
		anatomic contour			
Definition: A disorder characte	rized by swelling due to an excessive	e accumulation of fluid in the geni	als.		
Gynecomastia	Asymptomatic breast	Symptomatic (e.g., pain or	Severe symptoms; elective	-	-
	enlargement	psychosocial impact)	operative intervention indicated		
Definition: A disorder characte	rized by excessive development of the	ne breasts in males.			
Hematosalpinx	Minimal bleeding identified on	Moderate bleeding; medical	Severe bleeding; transfusion	Life-threatening consequences;	Death
	imaging study or laparoscopy;	intervention indicated	indicated; radiologic or	urgent operative intervention	
	intervention not indicated		endoscopic intervention	indicated	

	Rep	productive system and bi	reast disorders				
	Grade						
Adverse Event	1	2	3	4	5		
Definition: A disorder characteri	zed by the presence of blood in a fa	allopian tube.	Г	Γ			
Irregular menstruation	Intermittent menses with skipped menses for no more than 1 to 3 months	Intermittent menses with skipped menses for more than 4 to 6 months	Persistent amenorrhea for more than 6 months	-	-		
Definition: A disorder characteri	zed by irregular cycle or duration of	f menses.	T	Γ	1		
Lactation disorder	Mild changes in lactation, not significantly affecting production or expression of breast milk	Changes in lactation, significantly affecting breast production or expression of breast milk	-	-	-		
Definition: A disorder characteri	zed by disturbances of milk secretion	on. It is not necessarily related to p	pregnancy that is observed in fema	ales and can be observed in males	S.		
Menorrhagia	Mild; iron supplements indicated	Moderate symptoms; medical intervention indicated (e.g., hormones)	Severe; transfusion indicated; surgical intervention indicated (e.g., hysterectomy)	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteri	zed by abnormally heavy vaginal bl	eeding during menses.					
Nipple deformity	Asymptomatic; asymmetry with slight retraction and/or thickening of the nipple areolar complex	Symptomatic; asymmetry of nipple areolar complex with moderate retraction and/or thickening of the nipple areolar complex	-	-	-		
Definition: A disorder characteri	zed by a malformation of the nipple		•				
Oligospermia	Sperm concentration >48 million/mL or motility >68%	Sperm concentration 13 - 48 million/mL or motility 32 - 68%	Sperm concentration <13 million/mL or motility <32%	-	-		
Definition: A disorder characteri	zed by a decrease in the number of	f spermatozoa in the semen.					
Ovarian hemorrhage	Minimal bleeding identified on imaging study or laproscopy; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder characteri	zed by bleeding from the ovary.	'	•	•	'		
Ovarian rupture	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteri	' zed by tearing or disruption of the c	varian tissue.	,	'	'		
Ovulation pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-		
Definition: A disorder characteri ovarian follicle.	zed by marked discomfort sensatio	n in one side of the abdomen betv	veen menstrual cycles, around the	time of the discharge of the ovum	from the		
Pelvic floor muscle weakness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic, not interfering with bladder, bowel, or vaginal function; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteri	zed by a reduction in the strength o	of the muscles of the pelvic floor.	1	<u> </u>			
Pelvic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-		
Definition: A disorder characteri	zed by marked discomfort sensatio	n in the pelvis.	T	Γ	1		
Penile pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-		
Definition: A disorder characteri	zed by marked discomfort sensatio	· · · · · · · · · · · · · · · · · · ·	I	<u> </u>	ı		
Perineal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-		
Definition: A disorder characteri	zed by a sensation of marked disco	omfort in the area between the ger	nital organs and the anus.	Т			
Premature menopause	-	-	Present	-	-		
Definition: A disorder characteri Prostatic hemorrhage	zed by ovarian failure before the ac Minimal bleeding identified on imaging study; intervention not indicated	pe of 40. Symptoms include hot fla Moderate bleeding; medical intervention indicated	shes, night sweats, mood swings a Severe bleeding; transfusion indicated; radiologic or endoscopic intervention	and a decrease in sex drive. Life-threatening consequences; urgent operative intervention indicated	Death		

	T(C)	productive system and bi			
			Grade		I _
Adverse Event	1	2	3	4	5
Definition: A disorder characteriz	zed by bleeding from the prostate of	gland.		I	1
Prostatic obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characteriz stream, and incomplete emptying	• •	secondary to enlargement of the p	prostate gland. This results in voidi	ng difficulties (straining to void, slo	ow urine
Prostatic pain	Mild pain	Moderate pain; limiting	Severe pain; limiting self care	-	-
D-6-iti A didti-		instrumental ADL	ADL		
	red by a sensation of marked disco				
Scrotal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	zed by marked discomfort sensatio	n in the scrotal area.	T	ı	1
Spermatic cord hemorrhage	Minimal bleeding identified on imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteriz	ed by bleeding from the spermation	cord.	•	'	
Spermatic cord obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterize	red by blockage of the normal flow	•	1	I	I
Testicular disorder	Asymptomatic; clinical or	Symptomatic but not interfering	Severe symptoms; interfering	Life-threatening consequences;	Death
TOGROUIDI GISOTGEI	diagnostic observations only;	with urination or sexual	with urination or sexual function;	urgent intervention indicated	Dodui
	intervention not indicated	activities; intervention not indicated; limiting instrumental	limiting self care ADL; intervention indicated		
		ADL			
Definition: A disorder characteriz	ed by involvement of the testis.			<u> </u>	1
Testicular hemorrhage	Minimal bleeding identified on imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteriz	ed by bleeding from the testis.				
Testicular pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	red by a sensation of marked disco	omfort in the testis.	1	•	
Uterine fistula	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	red by an abnormal communication	n between the uterus and another	organ or anatomic site.	•	•
Uterine hemorrhage	Minimal bleeding identified on imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteriz	ed by bleeding from the uterus.	•	•	'	•
Uterine obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterize	zed by blockage of the uterine outle	1	1 .	ı	1
Uterine pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteria	l zed by a sensation of marked disco	•	I: ===	I	I
	Mild vaginal discharge (greater	Moderate to heavy vaginal	1_	_	l
	Ivilia vagillai discriarge (greater	discharge; use of perineal pad	-	-	-
	than baseline for patient)	or tampon indicated			
Vaginal discharge		or tampon indicated	discharged from the vagina natura	lly, especially during the childbear	l ring years
Vaginal discharge		or tampon indicated	discharged from the vagina natural Severe vaginal dryness resulting in dyspareunia or severe discomfort	lly, especially during the childbear	ring years

	Rep	roductive system and b	reast disorders		
			Grade		
Adverse Event	1	2	3	4	5
Vaginal fistula	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by an abnormal communication	between the vagina and another	organ or anatomic site.		
Vaginal hemorrhage	Minimal bleeding identified on clinical exam or imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterize	ed by bleeding from the vagina.				
Vaginal inflammation	Mild discomfort or pain, edema, or redness	Moderate discomfort or pain, edema, or redness; limiting instrumental ADL	Severe discomfort or pain, edema, or redness; limiting self care ADL; small areas of mucosal ulceration	Widespread areas of mucosal ulceration; life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by inflammation involving the v	agina. Symptoms may include rec	Iness, edema, marked discomfort	and an increase in vaginal dischar	ge.
Vaginal obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterize	ed by blockage of vaginal canal.				
Vaginal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterize	ed by a sensation of marked disco	mfort in the vagina.			
Vaginal perforation	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by a rupture in the vaginal wall.				
Vaginal stricture	Asymptomatic; mild vaginal shortening or narrowing	Vaginal narrowing and/or shortening not interfering with physical examination	Vaginal narrowing and/or shortening interfering with the use of tampons, sexual activity or physical examination	-	Death
Definition: A disorder characterize	ed by a narrowing of the vaginal ca	anal.			
Vaginismus	Mild discomfort or pain associated with vaginal spasm/tightening; no impact upon sexual function or physical examination	Moderate discomfort or pain associated with vaginal spasm/tightening; disruption in sexual function and physical examination	Severe discomfort or pain associated with vaginal spasm/tightening; unable to tolerate vaginal penetration or physical examination	-	-
Definition: A disorder characterize intercourse.	ed by involuntary spasms of the pe	elvic floor muscles, resulting in pa	thologic tightness of the vaginal w	all during penetration such as duri	ng sexual
Reproductive system and breast disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

	Respi	ratory, thoracic and med	iastinal disorders					
	Grade							
Adverse Event	1	2	3	4	5			
Adult respiratory distress syndrome	-	-	Present with radiologic findings; intubation not indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death			
Definition: A disorder characteri surgery.	zed by progressive and life-threater	ning pulmonary distress in the abs	sence of an underlying pulmonary	condition, usually following major t	rauma or			
Allergic rhinitis	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-			
	zed by an inflammation of the nasa of the sinuses, eyes, middle ear, a			-	ay also			
Apnea	-	-	Present; medical intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death			
Definition: A disorder characteri	1			l .				
Aspiration	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Altered eating habits; coughing or choking episodes after eating or swallowing; medical intervention indicated (e.g., suction or oxygen)	Dyspnea and pneumonia symptoms (e.g., aspiration pneumonia); hospitalization indicated; unable to aliment orally	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death			
Definition: A disorder characteri	zed by inhalation of solids or liquids	s into the lungs.			1			
Atelectasis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., dyspnea, cough); medical intervention indicated (e.g., chest physiotherapy, suctioning); bronchoscopic suctioning	Oxygen indicated; hospitalization or elective operative intervention indicated (e.g., stent, laser)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death			
Definition: A disorder characteri	zed by the collapse of part or the en	ntire lung.	1	T				
Bronchial fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical management indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death			
Definition: A disorder characteri	zed by an abnormal communication	between the bronchus and anoth	ner organ or anatomic site.					
Bronchial obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., mild wheezing); endoscopic evaluation indicated; radiographic evidence of atelectasis/lobar collapse; medical management indicated (e.g., steroids, bronchodilators)	Shortness of breath with stridor; endoscopic intervention indicated (e.g., laser, stent placement)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death			
Definition: A disorder characteri	zed by blockage of a bronchus pas	sage, most often by bronchial sec	retions and exudates.					
Bronchial stricture	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., rhonchi or wheezing) but without respiratory distress; medical intervention indicated (e.g., steroids, bronchodilators)	Shortness of breath with stridor; endoscopic intervention indicated (e.g., laser, stent placement)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death			
	zed by a narrowing of the bronchial		Sovoro gymntama: limitim - 15	Life threatening con	Doo#-			
Bronchopleural fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death			
Definition: A disorder characteri	zed by an abnormal communication	between a bronchus and the ple	ural cavity.	I				
Bronchopulmonary hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g.,	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention	Death			

	Kespii	ratory, thoracic and med			
			Grade		ı
Adverse Event	1	2	3	4	5
Bronchospasm	Mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Limiting self care ADL; oxygen saturation decreased	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder charact	erized by a sudden contraction of the	smooth muscles of the bronchial	wall.	T	
Chylothorax	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thoracentesis or tube drainage indicated	Severe symptoms; elective operative intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder charact	erized by milky pleural effusion (abnor	rmal collection of fluid) resulting fr	om accumulation of lymph fluid in	the pleural cavity.	
Cough	Mild symptoms; nonprescription intervention indicated	Moderate symptoms, medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder charact by a distinctive sound.	erized by sudden, often repetitive, spa	asmodic contraction of the thoraci	c cavity, resulting in violent release	e of air from the lungs and usually	accompani
Dyspnea	Shortness of breath with moderate exertion	Shortness of breath with minimal exertion; limiting instrumental ADL	Shortness of breath at rest; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder charact	erized by an uncomfortable sensation	of difficulty breathing.			
Epistaxis	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated (e.g., nasal packing, cauterization; topical vasoconstrictors)	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder charact	erized by bleeding from the nose.				
Hiccups	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe symptoms; interfering with sleep; limiting self care ADL	-	-
Definition: A disorder charact	erized by repeated gulp sounds that re	esult from an involuntary opening	and closing of the glottis. This is a	ttributed to a spasm of the diaphra	igm. I
Hoarseness	Mild or intermittent voice change; fully understandable; self-resolves	Moderate or persistent voice changes; may require occasional repetition but understandable on telephone; medical evaluation indicated	Severe voice changes including predominantly whispered speech	-	-
Definition: A disorder charact	erized by harsh and raspy voice arisin	ng from or spreading to the larynx.			
Hypoxia	-	Decreased oxygen saturation with exercise (e.g., pulse oximeter <88%); intermittent supplemental oxygen	Decreased oxygen saturation at rest (e.g., pulse oximeter <88% or PaO2 <=55 mm Hg)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
	erized by a decrease in the level of ox	i			
aryngeal edema.	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (e.g., dexamethasone, epinephrine, antihistamines)	Stridor; respiratory distress; hospitalization indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
	erized by swelling due to an excessive			1.55- 41	D- "
aryngeal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical management indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention indicated (e.g., thoracoplasty, chronic open drainage or multiple thoracotomies)	Death
Definition: A disorder charact	erized by an abnormal communication	between the larynx and another	organ or anatomic site.		
aryngeal hemorrhage	Mild cough or trace hemoptysis; laryngoscopic findings	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder charact	erized by bleeding from the larynx.	I	1	I	
_aryngeal inflammation	Mild sore throat; raspy voice	Moderate sore throat;	Severe throat pain; endoscopic	-	-

	Respi	ratory, thoracic and med	iastinal disorders			
			Grade			
Adverse Event	1	2	3	4	5	
Laryngeal mucositis	Endoscopic findings only; mild discomfort with normal intake	Moderate discomfort; altered oral intake	Severe pain; severely altered eating/swallowing; medical intervention indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death	
Definition: A disorder character	ized by an inflammation involving th	e mucous membrane of the laryn	(. I	Γ	1	
Laryngeal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids); limiting instrumental ADL	Limiting self care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder character	ized by blockage of the laryngeal ai	rway.				
Laryngeal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Limiting self care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening consequences; urgent intervention indicated	Death	
	ized by a narrowing of the laryngeal				D "	
Laryngopharyngeal dysesthesia	a Mild symptoms; no anxiety; intervention not indicated	Moderate symptoms; mild anxiety, but no dyspnea; short duration of observation and or anxiolytic indicated; limiting instrumental ADL	Severe symptoms; dyspnea and swallowing difficulty; limiting self care ADL	Life-threatening consequences	Death	
Definition: A disorder character	ized by an uncomfortable persistent	sensation in the area of the laryn	gopharynx.			
Laryngospasm	-	Transient episode; intervention not indicated	Recurrent episodes; noninvasive intervention indicated (e.g., breathing technique, pressure point massage)	Persistent or severe episodes associated with syncope; urgent intervention indicated (e.g., fiberoptic laryngoscopy, intubation, botox injection)	Death	
Definition: A disorder character	ized by paroxysmal spasmodic mus	cular contraction of the vocal cord		, ,	1	
Mediastinal hemorrhage	Radiologic evidence only; minimal symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder character	ized by bleeding from the mediastin	um.		'	'	
Nasal congestion	indicated	Moderate symptoms; medical intervention indicated	Associated with bloody nasal discharge or epistaxis	-	-	
	ized by obstruction of the nasal pas					
Pharyngeal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent intervention indicated	Death	
	ized by an abnormal communication		1			
Pharyngeal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death	
Definition: A disorder character	ized by bleeding from the pharynx.	T			1	
Pharyngeal mucositis	Endoscopic findings only; minimal symptoms with normal oral intake; mild pain but analgesics not indicated	Moderate pain and analgesics indicated; altered oral intake; limiting instrumental ADL	Severe pain; unable to adequately aliment or hydrate orally; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder character	ized by an inflammation involving th	e mucous membrane of the phary	nx.	Г	1	
Pharyngeal necrosis	-	-	Inability to aliment adequately by GI tract; tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death	

Respiratory, thoracic and mediastinal disorders							
	Grade						
Adverse Event	1	2	3	4	5		
Definition: A disorder character	ized by a necrotic process occurring	in the pharynx.					
Pharyngeal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids); limiting instrumental ADL	Limiting self care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death		
Definition: A disorder character	ized by a narrowing of the pharynge	al airway.	,	'	'		
Pharyngolaryngeal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-		
Definition: A disorder character	ized by marked discomfort sensation	n in the pharyngolaryngeal region.	1	1			
Pleural effusion	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; intervention indicated (e.g., diuretics or limited therapeutic thoracentesis)	Symptomatic with respiratory distress and hypoxia; surgical intervention including chest tube or pleurodesis indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death		
Definition: A disorder character	ized by an increase in amounts of flo	uid within the pleural cavity. Symp	toms include shortness of breath,	cough and marked chest discomfo	ort.		
Pleural hemorrhage	Asymptomatic; mild hemorrhage confirmed by thoracentesis	Symptomatic or associated with pneumothorax; chest tube drainage indicated	>1000 ml of blood evacuated; persistent bleeding (150-200 ml/hr for 2 - 4 hr); persistent transfusion indicated; elective operative intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death		
Definition: A disorder character	ized by bleeding from the pleural ca	vity.	•				
Pleuritic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-		
Definition: A disorder character	ized by marked discomfort sensation	n in the pleura.		1			
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death		
	ized by inflammation focally or diffus						
Pneumothorax	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; intervention indicated (e.g., tube placement without sclerosis)	Sclerosis and/or operative intervention indicated; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder character	ized by abnormal presence of air in	the pleural cavity resulting in the	collapse of the lung.				
Postnasal drip	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-		
Definition: A disorder character	ized by excessive mucous secretion	in the back of the nasal cavity or	throat, causing sore throat and/or	coughing.			
Productive cough	1	Moderate sputum production; limiting instrumental ADL	Persistent or copious production of sputum; limiting self care ADL		-		
	ized by expectorated secretions upo		0		D#-		
Pulmonary edema	Radiologic findings only; minimal dyspnea on exertion	Moderate dyspnea on exertion; medical intervention indicated; limiting instrumental ADL	Severe dyspnea or dyspnea at rest; oxygen indicated; limiting self care ADL	Life-threatening respiratory compromise; urgent intervention or intubation with ventilatory support indicated	Death		
Definition: A disorder character	ized by accumulation of fluid in the I	ung tissues that causes a disturba		lead to respiratory failure.			
Pulmonary fibrosis	Mild hypoxemia; radiologic pulmonary fibrosis <25% of lung volume	Moderate hypoxemia; evidence of pulmonary hypertension; radiographic pulmonary fibrosis 25 - 50%	Severe hypoxemia; evidence of right-sided heart failure; radiographic pulmonary fibrosis >50 - 75%	Life-threatening consequences (e.g., hemodynamic/pulmonary complications); intubation with ventilatory support indicated; radiographic pulmonary fibrosis >75% with severe honeycombing	Death		
Definition: A disorder character	ized by the replacement of the lung	tissue by connective tissue, leadir	ng to progressive dyspnea, respira	tory failure or right heart failure.			
Pulmonary fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical management indicated; limiting instrumental ADL	Limiting self care ADL; endoscopic stenting or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		

	Respi	ratory, thoracic and med	astinal disorders		
			Grade		
Adverse Event	1	2	3	4	5
Definition: A disorder characteriz	ed by an abnormal communication	between the lung and another or	gan or anatomic site.		
Pulmonary hypertension	Minimal dyspnea; findings on physical exam or other evaluation	Moderate dyspnea, cough; requiring evaluation by cardiac catheterization and medical intervention	Severe symptoms, associated with hypoxemia, right heart failure; oxygen indicated	Life-threatening airway consequences; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characteriz	ed by an increase in pressure with	in the pulmonary circulation due to	lung or heart disorder.		
Respiratory failure	-	-	-	Life-threatening consequences; urgent intervention, intubation, or ventilatory support indicated	Death
Definition: A disorder characteriz with an increase in arterial levels	red by impaired gas exchange by to s of carbon dioxide.	he respiratory system resulting in	hypoxemia and a decrease in oxy	genation of the tissues that may be	e associated
Retinoic acid syndrome	Fluid retention; <3 kg of weight gain; intervention with fluid restriction and/or diuretics indicated	Moderate signs or symptoms; steroids indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; ventilatory support indicated	Death
Definition: A disorder characteriz retinoic acid.	red by weight gain, dyspnea, pleur	al and pericardial effusions, leukoo	cytosis and/or renal failure original	ly described in patients treated wit	h all-trans
Sinus disorder	Asymptomatic mucosal crusting; blood-tinged secretions	Symptomatic stenosis or edema/narrowing interfering with airflow; limiting instrumental ADL	Stenosis with significant nasal obstruction; limiting self care ADL	Necrosis of soft tissue or bone; urgent operative intervention indicated	Death
Definition: A disorder characteriz	ed by involvement of the paranasa	al sinuses.			
Sleep apnea	Snoring and nocturnal sleep arousal without apneic periods	Moderate apnea and oxygen desaturation; excessive daytime sleepiness; medical evaluation indicated; limiting instrumental ADL	Oxygen desaturation; associated with hypertension; medical intervention indicated; limiting self care ADL	Cardiovascular or neuropsychiatric symptoms; urgent operative intervention indicated	Death
Definition: A disorder characteriz	ed by cessation of breathing for sh	nort periods during sleep.	•	'	•
Sneezing	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characteriz	ed by the involuntary expulsion of	air from the nose.	,	'	
Sore throat	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL; limiting ability to swallow	-	-
Definition: A disorder characteriz	ed by of marked discomfort in the	throat			
Stridor	-	-	Respiratory distress limiting self care ADL; medical intervention indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characteriz	ed by a high pitched breathing sou	und due to laryngeal or upper airw	ay obstruction.		
Tracheal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention indicated (e.g., thoracoplasty, chronic open drainage or multiple thoracotomies)	Death
Definition: A disorder characteriz	ed by an abnormal communication	between the trachea and anothe	organ or anatomic site.		
Tracheal mucositis	Endoscopic findings only; minimal hemoptysis, pain, or respiratory symptoms	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe pain; hemorrhage or respiratory symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
	ted by an inflammation involving th			I	<u> </u>
Tracheal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Stridor or respiratory distress limiting self care ADL; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characteriz	ed by a narrowing of the trachea.				

	Respi	ratory, thoracic and med	iastinal disorders					
	Grade							
Adverse Event	1	2	3	4	5			
Voice alteration	Mild or intermittent change from normal voice	Moderate or persistent change from normal voice; still understandable	Severe voice changes including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; may require assistive technology	-	-			
Definition: A disorder characteriz	ed by a change in the sound and/o	or speed of the voice.						
Wheezing	Detectable airway noise with minimal symptoms	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe respiratory symptoms limiting self care ADL; oxygen therapy or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteriz	ed by a high-pitched, whistling sou	ind during breathing. It results from	n the narrowing or obstruction of t	he respiratory airways.				
Respiratory, thoracic and mediastinal disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death			

Skin and subcutaneous tissue disorders Grade							
			Grade				
Adverse Event	1	2	3	4	5		
Alopecia	Hair loss of <50% of normal for	Hair loss of >=50% normal for	-	-	-		
	that individual that is not	that individual that is readily					
	obvious from a distance but only						
	on close inspection; a different	piece is necessary if the patient					
	hair style may be required to	desires to completely					
	cover the hair loss but it does	camouflage the hair loss;					
	not require a wig or hair piece to	associated with psychosocial					
	camouflage	impact					
Definition: A disorder characteriz	zed by a decrease in density of hair	compared to normal for a given in	ndividual at a given age and body	location.			
Body odor	Mild odor; physician intervention	Pronounced odor; psychosocial	-	-	-		
	not indicated; self care	impact; patient seeks medical					
	interventions	intervention					
Definition: A disorder characteriz	zed by an abnormal body smell res	ulting from the growth of bacteria	on the body.	I			
Bullous dermatitis	Asymptomatic; blisters covering	Blisters covering 10 - 30% BSA;	Blisters covering >30% BSA;	Blisters covering >30% BSA;	Death		
Bullous definiatins	<10% BSA	painful blisters; limiting	limiting self care ADL	associated with fluid or	Death		
	10 % BSA	instrumental ADL	lilling sell care ADL				
		monumental ADL		electrolyte abnormalities; ICU			
D 6 111 A 11 A 11 A 1 A 1 A 1 A 1 A 1 A 1				care or burn unit indicated	I		
	zed by inflammation of the skin cha				1		
Dry skin	Covering <10% BSA and no	Covering 10 - 30% BSA and	Covering >30% BSA and	-	-		
	associated erythema or pruritus	associated with erythema or	associated with pruritus; limiting				
		pruritus; limiting instrumental	self care ADL				
		ADL					
Definition: A disorder characteriz	zed by flaky and dull skin; the pores	are generally fine, the texture is	a papery thin texture.				
Erythema multiforme	Target lesions covering <10%	Target lesions covering 10 -	Target lesions covering >30%	Target lesions covering >30%	Death		
	BSA and not associated with	30% BSA and associated with	BSA and associated with oral or	BSA; associated with fluid or	2000.		
	skin tenderness	skin tenderness	genital erosions	electrolyte abnormalities; ICU			
	Skiii teliuelliess	skiii teriderriess	gerital erosions	care or burn unit indicated			
D 6 70 A 11 A 1 A 1				care or built utilit indicated	ı		
	zed by target lesions (a pink-red rin		I		T		
Erythroderma	-	Erythema covering >90% BSA	Erythema covering >90% BSA	Erythema covering >90% BSA	Death		
		without associated symptoms;	with associated symptoms (e.g.,	with associated fluid or			
		limiting instrumental ADL	pruritus or tenderness); limiting	electrolyte abnormalities; ICU			
			self care ADL	care or burn unit indicated			
Definition: A disorder characteriz	zed by generalized inflammatory er	ythema and exfoliation. The inflan	nmatory process involves > 90% o	f the body surface area.			
Fat atrophy	Covering <10% BSA and	Covering 10 - 30% BSA and	Covering >30% BSA;	-	-		
Fat atrophy	Covering <10% BSA and asymptomatic	Covering 10 - 30% BSA and associated with erythema or	Covering >30% BSA; associated with erythema or	-	-		
Fat atrophy		· ·		-	-		
Fat atrophy		associated with erythema or	associated with erythema or	-	-		
		associated with erythema or tenderness; limiting instrumental	associated with erythema or tenderness; limiting self-care		-		
Definition: A disorder characteriz	asymptomatic zed by shrinking of adipose tissue.	associated with erythema or tenderness; limiting instrumental ADL	associated with erythema or tenderness; limiting self-care	-	- -		
Definition: A disorder characteriz	asymptomatic zed by shrinking of adipose tissue. In women, increase in length,	associated with erythema or tenderness; limiting instrumental ADL In women, increase in length,	associated with erythema or tenderness; limiting self-care	-	-		
	asymptomatic zed by shrinking of adipose tissue. In women, increase in length, thickness or density of hair in a	associated with erythema or tenderness; limiting instrumental ADL In women, increase in length, thickness or density of hair in a	associated with erythema or tenderness; limiting self-care	-	-		
Definition: A disorder characteriz	asymptomatic zed by shrinking of adipose tissue. In women, increase in length, thickness or density of hair in a male distribution that the patient	associated with erythema or tenderness; limiting instrumental ADL In women, increase in length, thickness or density of hair in a male distribution that requires	associated with erythema or tenderness; limiting self-care	-	-		
Definition: A disorder characteriz	asymptomatic ed by shrinking of adipose tissue. In women, increase in length, thickness or density of hair in a male distribution that the patient is able to camouflage by	associated with erythema or tenderness; limiting instrumental ADL In women, increase in length, thickness or density of hair in a male distribution that requires daily shaving or consistent	associated with erythema or tenderness; limiting self-care	-	-		
Definition: A disorder characteriz	asymptomatic zed by shrinking of adipose tissue. In women, increase in length, thickness or density of hair in a male distribution that the patient is able to camouflage by periodic shaving, bleaching, or	associated with erythema or tenderness; limiting instrumental ADL In women, increase in length, thickness or density of hair in a male distribution that requires daily shaving or consistent destructive means of hair	associated with erythema or tenderness; limiting self-care	-	-		
Definition: A disorder characteriz	asymptomatic ed by shrinking of adipose tissue. In women, increase in length, thickness or density of hair in a male distribution that the patient is able to camouflage by	associated with erythema or tenderness; limiting instrumental ADL In women, increase in length, thickness or density of hair in a male distribution that requires daily shaving or consistent destructive means of hair removal to camouflage;	associated with erythema or tenderness; limiting self-care	-	-		
Definition: A disorder characteriz	asymptomatic zed by shrinking of adipose tissue. In women, increase in length, thickness or density of hair in a male distribution that the patient is able to camouflage by periodic shaving, bleaching, or	associated with erythema or tenderness; limiting instrumental ADL In women, increase in length, thickness or density of hair in a male distribution that requires daily shaving or consistent destructive means of hair removal to camouflage; associated with psychosocial	associated with erythema or tenderness; limiting self-care	-	-		
Definition: A disorder characteriz Hirsutism	asymptomatic zed by shrinking of adipose tissue. In women, increase in length, thickness or density of hair in a male distribution that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair	associated with erythema or tenderness; limiting instrumental ADL In women, increase in length, thickness or density of hair in a male distribution that requires daily shaving or consistent destructive means of hair removal to camouflage; associated with psychosocial impact	associated with erythema or tenderness; limiting self-care ADL	-	-		
Definition: A disorder characteriz Hirsutism Definition: A disorder characteriz	asymptomatic zed by shrinking of adipose tissue. In women, increase in length, thickness or density of hair in a male distribution that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair	associated with erythema or tenderness; limiting instrumental ADL In women, increase in length, thickness or density of hair in a male distribution that requires daily shaving or consistent destructive means of hair removal to camouflage; associated with psychosocial impact	associated with erythema or tenderness; limiting self-care ADL	- e a secondary male characteristic			
Definition: A disorder characteriz Hirsutism Definition: A disorder characteriz androgen control (beard, mousta	asymptomatic zed by shrinking of adipose tissue. In women, increase in length, thickness or density of hair in a male distribution that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair zed by the presence of excess hair ache, chest, abdomen)	associated with erythema or tenderness; limiting instrumental ADL In women, increase in length, thickness or density of hair in a male distribution that requires daily shaving or consistent destructive means of hair removal to camouflage; associated with psychosocial impact growth in women in anatomic site	associated with erythema or tenderness; limiting self-care ADL - s where growth is considered to b	- e a secondary male characteristic	c and under		
Definition: A disorder characteriz Hirsutism	asymptomatic zed by shrinking of adipose tissue. In women, increase in length, thickness or density of hair in a male distribution that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair zed by the presence of excess hair ache, chest, abdomen) Limited to one site (palms,	associated with erythema or tenderness; limiting instrumental ADL In women, increase in length, thickness or density of hair in a male distribution that requires daily shaving or consistent destructive means of hair removal to camouflage; associated with psychosocial impact growth in women in anatomic site Involving >1 site; patient seeks	associated with erythema or tenderness; limiting self-care ADL - s where growth is considered to b	e a secondary male characteristic	c and under		
Definition: A disorder characteriz Hirsutism Definition: A disorder characteriz androgen control (beard, mousta	asymptomatic zed by shrinking of adipose tissue. In women, increase in length, thickness or density of hair in a male distribution that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair zed by the presence of excess hair ache, chest, abdomen) Limited to one site (palms, soles, or axillae); self care	associated with erythema or tenderness; limiting instrumental ADL In women, increase in length, thickness or density of hair in a male distribution that requires daily shaving or consistent destructive means of hair removal to camouflage; associated with psychosocial impact growth in women in anatomic site Involving >1 site; patient seeks medical intervention; associated	associated with erythema or tenderness; limiting self-care ADL - s where growth is considered to b Generalized involving sites other than palms, soles, or	e a secondary male characteristic	- and under		
Definition: A disorder characteriz Hirsutism Definition: A disorder characteriz androgen control (beard, mousta	asymptomatic zed by shrinking of adipose tissue. In women, increase in length, thickness or density of hair in a male distribution that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair zed by the presence of excess hair ache, chest, abdomen) Limited to one site (palms,	associated with erythema or tenderness; limiting instrumental ADL In women, increase in length, thickness or density of hair in a male distribution that requires daily shaving or consistent destructive means of hair removal to camouflage; associated with psychosocial impact growth in women in anatomic site Involving >1 site; patient seeks	associated with erythema or tenderness; limiting self-care ADL - s where growth is considered to b	e a secondary male characteristic	c and und		
Definition: A disorder characteriz Hirsutism Definition: A disorder characteriz androgen control (beard, mousta	asymptomatic zed by shrinking of adipose tissue. In women, increase in length, thickness or density of hair in a male distribution that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair zed by the presence of excess hair ache, chest, abdomen) Limited to one site (palms, soles, or axillae); self care	associated with erythema or tenderness; limiting instrumental ADL In women, increase in length, thickness or density of hair in a male distribution that requires daily shaving or consistent destructive means of hair removal to camouflage; associated with psychosocial impact growth in women in anatomic site Involving >1 site; patient seeks medical intervention; associated	associated with erythema or tenderness; limiting self-care ADL - s where growth is considered to b Generalized involving sites other than palms, soles, or	e a secondary male characteristic	- and under		

Skin and subcutaneous tissue disorders								
			Grade		1			
Adverse Event	1	2	3	4	5			
Hypertrichosis	Increase in length, thickness or density of hair that the patient is either able to camouflage by periodic shaving or removal of hairs or is not concerned enough about the overgrowth to	Increase in length, thickness or density of hair at least on the usual exposed areas of the body [face (not limited to beard/moustache area) plus/minus arms] that requires	-	-	-			
	use any form of hair removal	frequent shaving or use of destructive means of hair removal to camouflage; associated with psychosocial impact						
Definition: A disorder characteria	zed by hair density or length beyon	d the accepted limits of normal in	a particular body region, for a part	icular age or race.				
Hypohidrosis	-	Symptomatic; limiting instrumental ADL	Increase in body temperature; limiting self care ADL	Heat stroke	Death			
Definition: A disorder characteri	T .				1			
Lipohypertrophy	Asymptomatic and covering <10% BSA	Covering 10 - 30% BSA and associated tenderness; limiting instrumental ADL	Covering >30% BSA and associated tenderness and narcotics or NSAIDs indicated; lipohypertrophy; limiting self care ADL	-	-			
Definition: A disorder characteria	zed by hypertrophy of the subcutan	eous adipose tissue at the site of	multiple subcutaneous injections of	of insulin.	,			
Nail discoloration	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-			
Definition: A disorder characteria	zed by a change in the color of the	nail plate.	T					
Nail loss	Asymptomatic separation of the nail bed from the nail plate or nail loss	Symptomatic separation of the nail bed from the nail plate or nail loss; limiting instrumental ADL	-	-	-			
Definition: A disorder characteri.	zed by loss of all or a portion of the	nail.						
Nail ridging	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-			
Definition: A disorder characteri:	zed by vertical or horizontal ridges	on the nails.	!					
Pain of skin	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characteria	zed by marked discomfort sensation	n in the skin.	T	T				
Palmar-plantar erythrodysesthesia syndrome	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL	Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self care ADL	-	-			
	zed by redness, marked discomfort			reet.	Τ			
Periorbital edema	Soft or non-pitting	Indurated or pitting edema; topical intervention indicated	Edema associated with visual disturbance; increased intraocular pressure, glaucoma or retinal hemorrhage; optic neuritis; diuretics indicated; operative intervention indicated	-	-			
Definition: A disorder characteri	zed by swelling due to an excessive	e accumulation of fluid around the	orbits of the face.					
Photosensitivity	Painless erythema and erythema covering <10% BSA	Tender erythema covering 10 - 30% BSA	Erythema covering >30% BSA and erythema with blistering; photosensitivity, oral corticosteroid therapy indicated; pain control indicated (e.g., narcotics or NSAIDs)	Life-threatening consequences; urgent intervention indicated	Death			

	- SK	in and subcutaneous tis		Grade							
Adverse Event	1	2	3	4	5						
Pruritus	Mild or localized; topical intervention indicated	Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts);	Intense or widespread; constant; limiting self care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated	-	-						
		oral intervention indicated; limiting instrumental ADL									
	zed by an intense itching sensation				1						
Purpura	Combined area of lesions covering <10% BSA	Combined area of lesions covering 10 - 30% BSA; bleeding with trauma	Combined area of lesions covering >30% BSA; spontaneous bleeding	-	-						
Definition: A disorder characteriz and eventually become a browni	zed by hemorrhagic areas of the sk ish-yellow color.	in and mucous membrane. Newe	r lesions appear reddish in color. C	Older lesions are usually a darker	purple color						
Rash acneiform	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; lifethreatening consequences	Death						
Definition: A disorder characteriz	ed by an eruption of papules and	oustules, typically appearing in fac	ce, scalp, upper chest and back.								
Rash maculo-papular	Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering >30% BSA with or without associated symptoms; limiting self care ADL	-	-						
	zed by the presence of macules (fla upper trunk, spreading centripetally		nown as morbillform rash, it is one	of the most common cutaneous a	dverse						
Scalp pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-						
Definition: A disorder characterization	zed by marked discomfort sensation	n in the skin covering the top and	the back of the head.								
Skin atrophy	Covering <10% BSA; associated with telangiectasias or changes in skin color	Covering 10 - 30% BSA; associated with striae or adnexal structure loss	Covering >30% BSA; associated with ulceration	-	-						
Definition: A disorder characteriz	ed by the degeneration and thinning	ng of the epidermis and dermis.									
Skin hyperpigmentation	Hyperpigmentation covering <10% BSA; no psychosocial impact	Hyperpigmentation covering >10% BSA; associated psychosocial impact	-	-	-						
Definition: A disorder characteriz	red by darkening of the skin due to	excessive melanin deposition.									
Skin hypopigmentation	Hypopigmentation or depigmentation covering <10% BSA; no psychosocial impact	Hypopigmentation or depigmentation covering >10% BSA; associated psychosocial impact	-	-	-						
Definition: A disorder characteriz	red by loss of skin pigment.										
Skin induration	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration, unable to slide or pinch skin; limiting joint movement or orifice (e.g., mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death						
Definition: A disorder characterize	red by an area of hardness in the s	kin.	1								
Skin ulceration	Combined area of ulcers <1 cm; nonblanchable erythema of intact skin with associated warmth or edema	Combined area of ulcers 1 - 2 cm; partial thickness skin loss involving skin or subcutaneous fat	Combined area of ulcers >2 cm; full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia	Any size ulcer with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures with or without full thickness skin loss	Death						

Skin and subcutaneous tissue disorders						
			Grade			
Adverse Event	1	2	3	4	5	
Stevens-Johnson syndrome	-	-	Skin sloughing covering <10% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment)	Skin sloughing covering 10 - 30% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment)	Death	
Definition: A disorder characterize	ed by less than 10% total body ski	n area separation of dermis. The	syndrome is thought to be a hyper	sensitivity complex affecting the s	kin and the	
mucous membranes.						
Telangiectasia	Telangiectasias covering <10% BSA	Telangiectasias covering >10% BSA; associated with psychosocial impact	-	-	-	
Definition: A disorder characterize	ed by local dilatation of small vess	els resulting in red discoloration o	f the skin or mucous membranes.			
Toxic epidermal necrolysis	-	-	-	Skin sloughing covering >=30% BSA with associated symptoms (e.g., erythema, purpura, or epidermal detachment)	Death	
Definition: A disorder characterize	ed by greater than 30% total body	skin area separation of dermis. T	he syndrome is thought to be a hy	persensitivity complex affecting th	e skin and the	
mucous membranes.						
Urticaria	Urticarial lesions covering <10% BSA; topical intervention indicated	Urticarial lesions covering 10 - 30% BSA; oral intervention indicated	Urticarial lesions covering >30% BSA; IV intervention indicated	-	-	
Definition: A disorder characterized by an itchy skin eruption characterized by wheals with pale interiors and well-defined red margins.						
Skin and subcutaneous tissue disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	

Social circumstances						
			Grade			
Adverse Event	1	2	3	4	5	
Menopause	Menopause occurring at age 46 - 53 years of age	, ,	Menopause occurring before age 40 years of age	-	-	
Definition: A disorder characteriz	ed by the permanent cessation of	menses, usually defined by 12 co	nsecutive months of amenorrhea i	n a woman over 45 years of age.		
Social circumstances - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	

Surgical and medical procedures						
		Grade				
Adverse Event	1	2	3	4	5	
Surgical and medical	Asymptomatic or mild	Moderate; minimal, local or	Severe or medically significant	Life-threatening consequences;	Death	
procedures - Other, specify	symptoms; clinical or diagnostic	noninvasive intervention	but not immediately life-	urgent intervention indicated		
	observations only; intervention	indicated; limiting age-	threatening; hospitalization or			
	not indicated	appropriate instrumental ADL	prolongation of existing			
			hospitalization indicated;			
			disabling; limiting self care ADL			

		Vascular disord	ers		
			Grade		
Adverse Event	1	2	3	4	5
Capillary leak syndrome	-	Symptomatic; medical intervention indicated	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	zed by leakage of intravascular fluid s syndromes, low-flow states, ischel			-	
failure.					
Flushing	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Symptomatic, associated with hypotension and/or tachycardia; limiting self care ADL	-	-
Definition: A disorder characteri	zed by episodic reddening of the fa	ce.		I	1
Hematoma	Mild symptoms; intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteri	zed by a localized collection of bloc	od, usually clotted, in an organ, sp	ace, or tissue, due to a break in th	e wall of a blood vessel.	
Hot flashes	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characteri	zed by an uncomfortable and temp	orary sensation of intense body w	armth, flushing, sometimes accom	panied by sweating upon cooling.	
Hypertension	Prehypertension (systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg)	Stage 1 hypertension (systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg); medical intervention indicated; recurrent or persistent (>=24 hrs); symptomatic increase by >20 mm Hg (diastolic) or to	Stage 2 hypertension (systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated Pediatric: Same as adult	Death
Definition: A disorder character	zed by a pathological increase in bl	>140/90 mm Hg if previously WNL; monotherapy indicated Pediatric: recurrent or persistent (>=24 hrs) BP >ULN; monotherapy indicated	Pediatric: Same as adult	ng 140 over 90 mm Ha	
Hypotension	Asymptomatic, intervention not	Non-urgent medical intervention	· · · · · · · · · · · · · · · · · · ·	Life-threatening and urgent	Death
,,	indicated	indicated	hospitalization indicated	intervention indicated	
Definition: A disorder characteri	zed by a blood pressure that is belo	ow the normal expected for an ind	ividual in a given environment.		
Lymph leakage	-	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	zed by the loss of lymph fluid into the	1	Ĺ		
Lymphedema	Trace thickening or faint discoloration	Marked discoloration; leathery skin texture; papillary formation; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characteri	zed by excessive fluid collection in	tissues that causes swelling.		T	
Lymphocele	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	-	-
Definition: A disorder characteri	zed by a cystic lesion containing ly	mph.			
Peripheral ischemia	-	Brief (<24 hrs) episode of ischemia managed non- surgically and without permanent deficit	Recurring or prolonged (>=24 hrs) and/or invasive intervention indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A disorder characteri	zed by impaired circulation to an ex	ctremity.	1	1	
Phlebitis	-	Present	-	-	-
Definition: A disorder characteri Superficial thrombophlebitis	zed by inflammation of the wall of a	vein. Present	-	-	-
	ा zed by a blood clot and inflammatio	1	e extremities	1	T

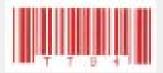
		Vascular disorde	ers			
			Grade			
Adverse Event	1	2	3	4	5	
Superior vena cava syndrome	Asymptomatic; incidental finding of SVC thrombosis	Symptomatic; medical intervention indicated (e.g., anticoagulation, radiation or chemotherapy)	Severe symptoms; multi- modality intervention indicated (e.g., anticoagulation, chemotherapy, radiation, stenting)	Life-threatening consequences; urgent multi-modality intervention indicated (e.g., lysis, thrombectomy, surgery)	Death	
Definition: A disorder characterized by obstruction of the blood flow in the superior vena cava. Signs and symptoms include swelling and cyanosis of the face, neck, and upper arms,						
cough, orthopnea and headache. Thromboembolic event	Venous thrombosis (e.g., superficial thrombosis)	Venous thrombosis (e.g., uncomplicated deep vein thrombosis), medical intervention indicated	Thrombosis (e.g., uncomplicated pulmonary embolism [venous], non-embolic cardiac mural [arterial] thrombus), medical intervention indicated	Life-threatening (e.g., pulmonary embolism, cerebrovascular event, arterial insufficiency); hemodynamic or neurologic instability; urgent intervention indicated	Death	
Definition: A disorder characterize	ed by occlusion of a vessel by a th	rombus that has migrated from a	distal site via the blood stream.			
Vasculitis	Asymptomatic, intervention not indicated	Moderate symptoms, medical intervention indicated	Severe symptoms, medical intervention indicated (e.g., steroids)	Life-threatening; evidence of peripheral or visceral ischemia; urgent intervention indicated	Death	
Definition: A disorder characterize	ed by inflammation involving the w	rall of a vessel.				
Visceral arterial ischemia	-	Brief (<24 hrs) episode of ischemia managed medically and without permanent deficit	Prolonged (>=24 hrs) or recurring symptoms and/or invasive intervention indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death	
Definition: A disorder characterize	ed by a decrease in blood supply o	due to narrowing or blockage of a	visceral (mesenteric) artery.			
Vascular disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	







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Appendix B: Pemphigus Disease Area Index (PDAI)

Pemphigus Disease Area Index (PDAI)

Skin	Activity		Damage Post-inflammatory	
Anatomical Locatio	Erosion/Blisters or new erythem	Erosion/Blisters or new erythema		
	0 absent 1 1-3 lesions, up to one >2 cm in any diameter, none > 6 cm 2 2-3 lesions, at least two > 2 cm diameter, none > 6cm 3 >3 lesions, none > 6 cm diameter 5 >3 lesions, and/or at least one >6 cm 10 >3 lesions, and/or at least one lesion >16 cm diameter or entire area	Number lesions if ≤ 3	from resolving lesion 0 absent 1 present	
Ears				
Nose				
Rest of the face				
Neck				_
Chest				
Abdomen				_
Back, buttocks				
Arms				_
Hands				_
Legs				_
Feet				_
Genitals				
Total skin	/120		/12	_
Scalp				
Scalp	Erosion/Blisters or new erythem	Post-inflammatory hyperpigmentation or erythe from resolving lesion	ma	
	0 absent 1 in one quadrant 2 two quadrants 3 three quadrants 4 affects whole skull 10 at least one lesion > 6 cm		0 absent 1 present	
Total Scalp (0-10)	/10		И	
Mucous mer	nbrane			
Anatomical Location	Erosion/Blisters			
	0 absent 1 1 lesion 2 2–3 lesions 5 >3 lesions or 2 lesions >2 cm 10 entire area	Number lesions if ≤ 3		
Eyes				
Nose				
Buccal mucosa				
Hard palate				
Soft palate				
Upper gingiva				
Lower gingiva				
Tongue		\vdash		
Floor of mouth				
Floor of mouth Labial bucosa				
Floor of mouth Labial bucosa Posterior pharynx				
Floor of mouth Labial bucosa	/120			

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Syntimmune, Inc.

SUMMARY OF CHANGES TO CLINICAL STUDY PROTOCOL

A Phase 1b, Multicenter, Open-Label, Safety, Tolerability, and Activity Study of SYNT001 in Subjects with Chronic Pemphigus (Vulgaris or Foliaceus)

Protocol Number: SYNT001-103

IND Number: 132727

Study Drug: SYNT001

Sponsor: Syntimmune, Inc.

257 Park Avenue South

15th Floor

New York, NY 10010

Medical Monitor:

Wallace House

17-21 Maxwell Place Stirling, Scotland FK81JU

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ext. PPD

Original Protocol:19 December 2016Amendment 1.118 January 2017Amendment 2.012 April 2017Amendment 3.010 October 2017

Confidentiality Statement

The information contained herein is confidential and the proprietary property of Syntimmune, Inc. and any unauthorized use or disclosure of such information without the prior written authorization of Syntimmune is expressly prohibited.

SUMMARY

The SYNT001-103 protocol has been amended under version 3.0 as follows:

- Medical Monitor and emergency contact information has been updated
- Clarification of allowable corticosteroids
- Additional exploratory biomarker and subsequent increase in total blood volume included
- Increase maximum BMI from 35.0 to 39.9 mg/m²
- Allowance of urine or serum pregnancy tests for women of childbearing potential at screening
- Clarification of the restriction on cellular therapy
- Provide guidance on the use of premedications for SYNT001 dosing
- Clarification of the type of skin the optional biopsies may be taken from
- Clarification of the method of sample collection for FCGR2A
- Clarification of the treatment for the single Grade 2 AE in the Phase 1a study
- Clarification of the data collected as part of the patient relevant medical history
- Removal of RR Interval as a required part of the ECG assessments
- Clarification that subjects exceeding a specific weight are not to be enrolled into the 30 mg/kg or higher dose groups based on theoretical host cell DNA levels per dose
- Clarification for the management of a Grade 1 infusion reaction.
- Provides a maximum duration of infusion in accordance with the requirements for SYNT001 preparation and administration outlined in the pharmacy manual
- Clarification of SAE reporting requirements and IRB notifications
- Sponsor contact information has been updated
- Various typographical and formatting corrections as well as corrections for consistency made throughout the document.

Syntimmune, Inc. Page 2 of 16 10 October 2017

SPECIFIC CHANGES

Text deletions are shown using strike through font; new text added in *italic font*. Listed page numbers are based on Protocol Amendment 2.0, dated 12 April 2017.

	ction, Page Number		Original Text	Revised Text	Rationale
Cover,	page 1	Blythe Tl	nomson, MD	Richard Kay, MD	Medical Monitor information updated
			PP PP reet,	Wallace House	
	D D	Cambridg	D D 01240	17-21 Maxwell Place	
				Stirling, Scotland FK81JU	
				Mobile Phone: (+44) 7747 621 827	
		PP D		Office Phone: (+44) 1786 460 400 ext.	
PP		PP		24461	
EmeD	cy Contact	BlyD	om , MD	Richard Kay, MD	Medical Monitor information updated
Info	tion, page 3	b.tl	@medpace.com	_r.kay@medpace.com	
		Μc	one: 1-513-748-2122	Mobile phone: (+44) 7747 621 827	
		PP D	ne: 1-PP -579-9911 ext.	Office phone: (+44) 1786 460 400 ext.	
				24461	
Synops				Exploratory biomarkers to	Added an additional exploratory objective to
Explor	•			investigate immune response	investigate other possible biomarkers associated
Objecti	ives, page 7			associated with pemphigus	with the pemphigus immune response
Synops	sis, Diagnosis	c. If bein	PP PP d with corticosteroids,	c. If being treated with corticosteroids,	Clarification of allowable corticosteroids
and ma	in entry	dose mp	D mg/kg/day and stable	dose must be $\leq 1 \text{mg/kg/day } of$	
	, page 9	(< 10 n)	n dose) for 2 weeks	prednisone or equivalent and stable (<	
PP D		pri	g	10% change in dose) for 2 weeks prior	
				to screening	
Sync	s, Diagnosis	5.	ass index (BMI) 18.5 – 35.0	5. Body mass index (BMI) 18.5 –	Patients who may be otherwise eligible to
and	entry	kg/		39.9 35.0 kg /m ² ;	participate in the study are excluded due to BMI.
crite	page 9		PP		We would like to be able to offer these
			D		individuals the opportunity to participate
-	s, Diagnosis	6.	egativ rine pregnancy test	6 Has a negative urine pregnancy test	Allows for serum or urine tests as per
	in entry	*	en of childbearing potential)	(for women of childbearing potential)	institutional standards
criteria	, page 9		ted prior to the first dose of	documented prior to the first dose of	
		study dru	<u> </u>	study drug;	
	sis, Diagnosis	10. Cellu	lar therapy at any time prior	10. Cellular therapy, <i>including CAR-T</i> ,	To further clarify the restriction on all cellular
	in entry	to screen	ing	therapy at any time prior to screening	therapy
criteria	, page 10				

Syntimmune, Inc. Page 4 of 16 10 October 2017

Confidential and Proprietary

Section, Page Number	Original Text	Revised Text	Rationale
Synopsis, Prohibited Concomitant Treatments, page 11	All treatments a subject receives within 14 days prior to enrollment through the end of the study will be documented. Concomitant medication and treatment for co-existing conditions, including those for pemphigus, are permitted if not excluded below. Topical antibiotics are permitted to treat active infections that occur on study. Topical or systemic treatments for oral candidiasis are permitted. Topical lidocaine for transient pain relief is acceptable as needed. Significant increases in anti-pemphigus medications will result in subjects being discontinued from the study. Concomitant treatment that is medically indicated for any AEs the subject experiences during the study are permitted.	All treatments a subject receives within 14 days prior to enrollment through the end of the study will be documented. Concomitant medication and treatment for co-existing conditions, including those for pemphigus, are permitted if not excluded below. Topical antibiotics are permitted to treat active infections that occur on study. Topical or systemic treatments for oral candidiasis are permitted. Topical lidocaine for transient pain relief is acceptable as needed. Significant increases in anti-pemphigus medications will result in subjects being discontinued from the study. Concomitant treatment that is medically indicated for any AEs the subject experiences during the study are permitted. Premedication is discouraged as prophylaxis against AEs or infusion reactions unless medically indicated from either past medical history, prior infusion reactions or AEs resulting from SYNT001 infusions.	Infusion reactions are a common adverse effect of IV administration of some, but not all monoclonal antibodies (mAb). Infusion reactions most commonly occur with the first infusion and are often related to the infusion rate. For mAbs with frequent infusion reactions, it is recommended that pre-medications, such as corticosteroids, acetaminophen and/or antihistamines, are administered prior to infusion, especially with the first infusion. However, pre-medications are generally not recommended for mAbs associated with no or mild infusion reactions. No infusion reactions occurred in the recently completed healthy volunteer phase 1a single-ascending dose study, where infusions were given over 1 hour at doses up to 30 mg/kg. As such, Syntimmune does not currently believe that it is necessary or appropriate to administer pre-medications to patients who will be receiving SYNT001 at the same doses and infusion rate as in the phase 1a study. If frequent infusion reactions are observed in the phase 1b study, the issue of pre-medication will be revisited.

Section, Page	Original Text	Revised Text	Rationale
Number			
Pharmacodynamics/	PD samples will be collected for	PD samples will be collected for	Added an additional exploratory objective to
Activity, page 13	analysis of IgG (serial assessment of	analysis of IgG (serial assessment of	investigate other possible biomarkers associated
	IgG levels to identify Cmin, Tmin);	IgG levels to identify Cmin, Tmin);	with the pemphigus immune response
	IgG1-4 subtype levels; IgA levels; IgM	IgG1-4 subtype levels; IgA levels; IgM	
	levels; albumin levels; anti-Dsg (1 and	levels; albumin levels; anti-Dsg (1 and	
	3) antibody levels; serum AECA by	3) antibody levels; serum AECA by	
	direct immunofluorescence; CIC; C3;	direct immunofluorescence; CIC; C3;	
	exploratory biomarkers (FCGR2A	exploratory biomarkers (FCGR2A	
	SNP, RNAseq, urine IgG, CD3+CD4+	SNP, RNAseq, urine IgG, CD3+CD4+	
	T, CD3+CD8+ T, monocytes, NK cells	T, CD3+CD8+ T, monocytes, NK cells	
	and B cells).	and B cells) and additional exploratory	
		analyses to investigate immune	
		response associated with pemphigus.	
Synopsis, Skin	Optional skin biopsy samples will be	Optional skin biopsy samples from	Clarifies type of skin the optional biopsies may
Biopsy, page 13	collected on Day 0 pre-dose and on	lesional or non-lesional skin will be	be taken from
	Days 1, 2, 14, 33, 56 and 84 to analyze	collected on Day 0 pre-dose and on	
	SYNT001 levels.	Days 1, 2, 14, 33, 56 and 84 to analyze	
		SYNT001 levels.	
Criteria for		• Exploratory biomarkers to investigate	Added an additional exploratory objective to
Evaluation, page 14		immune response associated with	investigate other possible biomarkers associated
		pemphigus	with the pemphigus immune response
Table 1, Study		Pemphigus immune response	Sample collection for exploratory pemphigus
Assessments, page 16		biomarkers	immune response biomarkers added at Days 0,
			5, 7, 12, 14, 19, 21, 28, 33, 42, 56, 84 and 112
Table 1, Study	FCGR2A ^m	FCGR2A ^m by buccal swab	Clarifies method of sample collection
Assessments, page 16			
Table 1, Study	m: Samples to be collected and stored;	m: Buccal Samples to be collected	Clarifies method of sample collection
Assessments, page 17	pending review of clinical and	and stored; pending review of clinical	
	pharmacodynamics assessments	and pharmacodynamics assessments	

Section, Page Number	Original Text	Revised Text	Rationale
Section 2.2, Selection	No AEs were observed in the 1 and 3	No AEs were observed in the 1 and 3	Clarifies that no treatment was given for the
of Doses in this	mg/kg dose cohorts. A single Grade 2	mg/kg dose cohorts. A single Grade 2	Grade 2 AE of headache in the Phase 1a study.
Study, page 27	AE was observed; a headache in the 10	AE was observed; a headache in the 10	-
	mg/kg cohort., treated with	mg/kg cohort-treated with	
	acetaminophen.	acetaminophen	
Section 3.3,		o Exploratory biomarkers to	Added an additional exploratory objective to
Exploratory		investigate immune response associated	investigate other possible biomarkers associated
Objectives, Page 29		with pemphigus	with the pemphigus immune response
Section 4.2,		• Exploratory biomarkers to investigate	Added an additional exploratory objective to
Exploratory Outcome		immune response associated with	investigate other possible biomarkers associated
Measures, page 31		pemphigus	with the pemphigus immune response
Section 5.2, Inclusion	c. If being treated with corticosteroids,	c. If being treated with corticosteroids,	Clarification of allowable corticosteroids
Criteria, page 34	dose must be $\leq 1 \text{mg/kg/day}$ and stable	dose must be $\leq 1 \text{mg/kg/day } of$	
	(< 10% change in dose) for 2 weeks	prednisone or equivalent and stable (<	
	prior to screening	10% change in dose) for 2 weeks prior	
		to screening	
Section 5.2, Inclusion	5. Body mass index (BMI) 18.5 – 35.0	5. Body mass index (BMI) 18.5 –	Patients who may be otherwise eligible to
Criteria, page 35	kg/m2;	<i>39.9</i> 35.0 kg/m2;	participate in the study are excluded due to BMI.
			We would like to be able to offer these
			individuals the opportunity to participate
Section 5.2, Inclusion	6. Has a negative urine pregnancy test	6. Has a negative urine pregnancy test	Allows for serum or urine tests as per
Criteria, page 35	(for women of childbearing potential)	(for women of childbearing potential)	institutional standards
	documented prior to the first dose of	documented prior to the first dose of	
	study drug;	study drug;	
Section 5.3,	10. Cellular therapy at any time prior	10. Cellular therapy, including CAR-T,	To further clarify the restriction on all cellular
Exclusion Criteria,	to screening	at any time prior to screening	therapy
page 36			

Section, Page Number	Original Text	Revised Text	Rationale
Section 6.2, Demographics and Medical History, page 37	Demographics (age, gender, race and ethnicity) and medical history will be obtained from the subject and recorded on the source document and eCRF. Medical history will capture the subject's current medical history (current disease processes), past medical status (past disease processes), history of surgery, transfusions and concomitant treatments.	Demographics (age, gender, race and ethnicity) and medical history will be obtained from the subject and recorded on the source document and eCRF. Medical history will capture the subject's current medical history (current disease processes), past medical status (past disease processes), history of surgery, transfusions and concomitant treatments, including relevant clinical response to past disease specific treatments and duration as well as dosing of such treatments.	Clarifies data collected as part of the patient relevant medical history
Section 6.6, 12-Lead Electrocardiogram (ECG), page 38	The following ECG parameters will be collected: PR interval, RR interval, QRS interval, and QT interval. The ECG findings will be evaluated by a qualified physician for the presence of abnormalities (qualitative assessment). The physician will assess each ECG as normal, abnormal/not clinically significant, or abnormal/clinically significant.	The following ECG parameters will be collected: PR interval, RR interval, QRS interval, and QT interval. The ECG findings will be evaluated by a qualified physician for the presence of abnormalities (qualitative assessment). The physician will assess each ECG as normal, abnormal/not clinically significant, or abnormal/clinically significant.	Not all study sites have ECG machines that report the RR interval. As heart rate is already being collected as part of clinical evaluation of vital signs, this measure does not provide additional information. ECG machines do provide an estimated heart rate over a 10-second recording and this is a more clinically meaningful outcome measure.
Section 6.7, Clinical Laboratory Measurements, page 39	The total blood draw for each subject who completes the study at Day 112, will be approximately 381 mL.	The total blood draw for each subject who completes the study at Day 112, will be approximately 381-433 mL.	Increase due to additional sample collection
Section 6.7.5, Table 4, Pharmacodynamic Sampling, page 42	Exploratory biomarker (FCGR2A SNP)	• Exploratory biomarker (FCGR2A SNP, via buccal swab)	Clarifies method of sample collection

Section, Page Number	Original Text	Revised Text	Rationale
Section 6.7.5, Table 4, Pharmacodynamic Sampling, page 42		• Exploratory pemphigus immune response Days, 0, 7, 14, 21, 28, 33, 42, 56, 84, 112	Sample collection for exploratory pemphigus immune response biomarkers added at Days 0, 5, 7, 12, 14, 19, 21, 28, 33, 42, 56, 84 and 112
Section 6.9, Prior and Concomitant Medications, page 43	All medications a subject receives within 14 days prior to enrollment through the end of the study will be documented on the source document and eCRF.	All medications a subject receives within 14 days prior to enrollment through the end of the study will be documented on the source document and eCRF. A history of treatments taken for primary disease, even if not taken within the 14 days prior to enrollment, will be collected.	Clarifies data collected as part of the patient relevant medical history
Section 6.12, Skin Biopsy, page 44	Optional skin biopsy samples will be collected on Day 0 pre-dose and on Days 1, 2, 14, 33, 56 and 84 to analyze SYNT001 levels	Optional skin biopsy samples <i>from lesional or non-lesional skin</i> will be collected on Day 0 pre-dose and on Days 1, 2, 14, 33, 56 and 84 to analyze SYNT001 levels	Clarifies type of skin biopsies may be taken from
Section 7.2, Enrollment and First Treatment: Dose 0, page 46	• FCGR2A SNP	FCGR2A SNP via buccal swab	Clarifies method of sample collection
Section 7.2, Enrollment and First Treatment: Dose 0, page 46		Exploratory pemphigus immune response biomarkers	Added an additional exploratory objective to investigate other possible biomarkers associated with the pemphigus immune response
Section 7.5, Follow- up Day 5, page 48		Exploratory pemphigus immune response biomarkers	Added an additional exploratory objective to investigate other possible biomarkers associated with the pemphigus immune response
Section 7.6, Treatment Day 7 (Dose 2), page 48		Exploratory pemphigus immune response biomarkers	Added an additional exploratory objective to investigate other possible biomarkers associated with the pemphigus immune response

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Section, Page Number	Original Text		Revised Text	Rationale
Section 7.7, Dose 2		•	Exploratory pemphigus immune	Added an additional exploratory objective to
Follow-up Day 12,			response biomarkers	investigate other possible biomarkers associated
page 49				with the pemphigus immune response
Section 7.8,		•	Exploratory pemphigus immune	Added an additional exploratory objective to
Treatment Day 14			response biomarkers	investigate other possible biomarkers associated
(Dose 3), page 50				with the pemphigus immune response
Section 7.9, Dose 3		•	Exploratory pemphigus immune	Added an additional exploratory objective to
Follow-up Day 19,			response biomarkers	investigate other possible biomarkers associated
page 51				with the pemphigus immune response
Section 7.10,		•	Exploratory pemphigus immune	Added an additional exploratory objective to
Treatment Day 21			response biomarkers	investigate other possible biomarkers associated
(Dose 4), page 51				with the pemphigus immune response
Section 7.11,		•	Exploratory pemphigus immune	Added an additional exploratory objective to
Treatment Day 28			response biomarkers	investigate other possible biomarkers associated
(Dose 5), page 52				with the pemphigus immune response
Section 7.14, Follow-		•	Exploratory pemphigus immune	Added an additional exploratory objective to
up Day 33, page 54			response biomarkers	investigate other possible biomarkers associated
				with the pemphigus immune response
Section 7.15, Follow-		•	Exploratory pemphigus immune	Added an additional exploratory objective to
up Day 42, page 55			response biomarkers	investigate other possible biomarkers associated
				with the pemphigus immune response
Section 7.16, Follow-		•	Exploratory pemphigus immune	Added an additional exploratory objective to
up Day 56, page 56			response biomarkers	investigate other possible biomarkers associated
				with the pemphigus immune response
Section 7.17, Follow-		•	Exploratory pemphigus immune	Added an additional exploratory objective to
up Day 84, page 56			response biomarkers	investigate other possible biomarkers associated
				with the pemphigus immune response
Section 7.18, Follow-		•	Exploratory pemphigus immune	Added an additional exploratory objective to
up Day 112, page 57			response biomarkers	investigate other possible biomarkers associated
				with the pemphigus immune response

Section, Page	Original Text	Revised Text	Rationale
Number			
Section 9.1, SYNT001, page 61	The specification for host cell DNA in SYNT001 is < 2 pg/mg, the limit of quantitation of the assay. To comply with regulatory guidelines, which specify a maximum level of 10 ng host cell DNA per dose, dosing is limited to 5000 mg SYNT001. Therefore, at the highest dose possible in this study (45 mg/kg), maximum subject weight will be limited to 111 kg.	The specification for host cell DNA in SYNT001 is < 2 pg/mg, the limit of quantitation of the assay. To comply with regulatory guidelines, which specify a maximum level of 10 ng host cell DNA per dose, dosing is limited to 5000 mg SYNT001. Therefore, the maximum subject weight allowed for enrollment into the 30 mg/kg dose cohort is 166 kg and the maximum subject weight allowed for enrollment into the highest dose possible in this study (45 mg/kg), maximum subject	Clarifies that subjects exceeding a specific weight are not to be enrolled into the 30 mg/kg or higher dose groups based on theoretical host cell DNA levels per dose.
		weight will be limited to is 111 kg.	

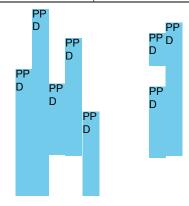
Section, Page Number	Original Text	Revised Text	Rationale
Section 9.6.1, Infusion Reaction, page 63	Management of Grade 1 infusion reactions include decreasing the rate of infusion by 50% and observing. Symptoms may also be treated as needed with medications such as diphenhydramine, hydrocortisone or acetaminophen. Management of Grade 2 and higher infusion reactions should include stopping the infusion of study drug. See Figure 1 and Figure 2 for details on the management of Grades 1- 2 and Grade 3 infusion reactions. The severity of and management of allergic or infusion-related reactions will be graded and managed using NCI CTCAE Version 4.03 (see Table 5).	Management of Grade 1 infusion reactions include <i>interrupting the infusion or</i> decreasing the rate of infusion by 50% and observing. Symptoms may also be treated as needed with medications such as diphenhydramine, hydrocortisone or acetaminophen, <i>either alone or in combination, depending on the subject's signs and symptoms. If the infusion is interrupted or the infusion rate is decreased, it is important to note that all study drug infusions must be completed within 4 hours of SYNT001 administration. Management of Grade 2 and higher infusion reactions should include stopping the infusion of study drug. See Figure 1 and Figure 2 for details on the management of Grades 1– 2 and Grade 3 infusion reactions. The severity of and management of allergic or infusion-related reactions will be graded and managed using NCI CTCAE Version 4.03 (see Table 5).</i>	Provides clarification for the management of a Grade 1 infusion reaction. Provides a maximum duration of infusion in accordance with the requirements for SYNT001 preparation and administration outlined in the pharmacy manual.
Section 9.6.1, Figure 1 Title, page 64	Management of Mild (Grade 1) to Moderate (Grade 2) Infusion Reactions	Management of Mild (Grade 1) to Moderate (Grade 2) Infusion Reaction	To be consistent with prior section regarding management of a Grade 1 infusion reaction and with CTCAE v4.03 definition of a Grade 1 infusion reaction.

Section, Page	Original Text	Revised Text	Rationale
Number			
Section 9.6.1, Figure 1, last box, page 64	Consider pre-medicating the subject with the same medication(s) 20-30	Consider pre-medicating the subject with the same medication(s) 20-30	Provision of a maximum duration of infusion in accordance with the requirements for SYNT001
	minutes in advance of subsequent administrations of SYNT001 and starting infusion at 50% of the planned	minutes in advance of subsequent administrations of SYNT001 and starting infusion at 50% of the planned	preparation and administration as outlined in the pharmacy manual.
	infusion rate for the first 30 minutes, then returning to the intended infusion rate in the absence of any infusion	infusion rate for the first 30 minutes, then returning to the intended infusion rate in the absence of any infusion	
	reaction	reaction. If the infusion is interrupted or the infusion rate is decreased, it is important to note that all study drug infusions must be completed within 4 hours of SYNT001 administration.	

Section, Page Number	Original Text	Revised Text	Rationale
Section 10, Concomitant Medication and Treatment, page 69	All treatments a subject receives within 14 days prior to enrollment through the end of the study will be documented. Concomitant medication and treatment for co-existing conditions, including those for pemphigus, are permitted if not excluded below. Topical antibiotics are permitted to treat active infections that occur on study. Topical or systemic treatments for oral candidiasis are permitted. Topical lidocaine for transient pain relief is acceptable as needed. Significant increases in anti-pemphigus medications will result in subjects being discontinued from the study. Concomitant treatment that is medically indicated for any AEs the subject experiences during the study are permitted.	All treatments a subject receives within 14 days prior to enrollment through the end of the study will be documented. Concomitant medication and treatment for co-existing conditions, including those for pemphigus, are permitted if not excluded below. Topical antibiotics are permitted to treat active infections that occur on study. Topical or systemic treatments for oral candidiasis are permitted. Topical lidocaine for transient pain relief is acceptable as needed. Significant increases in anti-pemphigus medications will result in subjects being discontinued from the study. Concomitant treatment that is medically indicated for any AEs the subject experiences during the study are permitted. Premedication is discouraged as prophylaxis against AEs or infusion reactions unless medically indicated from either past medical history, prior infusion reactions or AEs resulting from SYNT001 infusions.	Infusion reactions are a common adverse effect of IV administration of some, but not all monoclonal antibodies (mAb). Infusion reactions most commonly occur with the first infusion and are often related to the infusion rate. For mAbs with frequent infusion reactions, it is recommended that pre-medications, such as corticosteroids, acetaminophen and/or antihistamines, are administered prior to infusion, especially with the first infusion. However, pre-medications are generally not recommended for mAbs associated with no or mild infusion reactions. No infusion reactions occurred in the recently completed healthy volunteer phase 1a single-ascending dose study, where infusions were given over 1 hour at doses up to 30 mg/kg. As such, Syntimmune does not currently believe that it is necessary or appropriate to administer pre-medications to patients who will be receiving SYNT001 at the same doses and infusion rate as in the phase 1a study. If frequent infusion reactions are observed in the phase 1b study, the issue of pre-medication will be revisited.

Section, Page Number	Original Text	Revised Text	Rationale
Section 11.3.9.1, Governing Regulatory Requirements, page 76	Written submission must be made by the sponsor to the FDA and the IRBs as soon as possible and in no event later than 15 calendar days after the sponsor's initial notification of the event. The sponsor shall also inform all Investigators.	Written submission must be made by the sponscPP the F ppp the IRBs as sooD pc le pp that ca pp that ca pp spo 's D n o eve Th pp the IRBs as vePP ater thc n o pp rm pp rm pp sti	Clarifies that notification to IRBs is not a responsibility of the sponsor.
Section 11.3.9.2, Time Frame for Reporting, page 76	Any death, SAE, pregnancy, or unexpected (and severe) AE experienced by the subject after informed consent through the last study	PP, S or xpt d (t sev erienced t he s rmed consent th he last study	Clarifies that adverse (severe) events that are not considered SAEs do not need to be reported within 24 hours but reported per section 11.3.6.
	visit, regardless of relationship to study drug, must be promptly reported (within 24 hours of the Investigator becoming aware of the event) by telephone or electronic transmission to the sponsor (or designee).	t, regardless of reachip to study drug, must be promptly reported (within 24 hours of the Investigator becoming awpp tele pp the pp the pp nsc hip to study nty pp PPD nt) by sm PP on to p	
Section 11.3.9.2, Time Frame for Reporting, page 77	Medical Safety Contact Blythe Thomson MD Medical Monitor Phone (US): 1-513-579-9911 extension 27201 Mobile phone: 1-513-748-2122 Email: b.thomson@medpace.com	Me IS K PPD K PPD K PPD D N NS: 244 bile phone 44) ail: r.kay@medp	Medical Monitor information updated
Section 14, Study Administration, Table 6, page 86	Sponsor Contact: Ryan Iarrobino SVP Clinical Operations and Data Management Phone: 617-913-1681 Email: ryan@syntimmune.com	nsor Contact: Ry robino SVP Clinical Operations and Data Management Phone: 617-913-1681 Email: ryan@syntimmune.com	Sponsor contact information updated

Section, P Numbe	_		Original Text		Revised Text	Rationale
Section 14,PP	dy		Sponsor Medical Direc	ctor:	Sponsor Contact and Medical Director:	Sponsor contact information updated
AdministraD	,		Laurence Blumberg, M	I D	Laurence Blumberg, MD	
Table 6, pa	6 PP		Founder and Chief Op	erating Officer	President and Chief Operating Officer	
	D		Phone: 917-4-22PP		Phone: 917-415-2210	
PP			Email: laur D nti D	ne.com	Email: laur@syntimmune.com	
Section	PP		Blythe Thom		Richard Kay, MD	Medical Monitor information updated
Admini	D	PP	Medpace		Medpace	
Table 6		D	43 Thorndike ee		Wallace House	
			Cambridge, 01		17-21 Maxwell Place	
				xt.27201	Stirling, Scotland FK81JU	
			Email: b.thoms PP m	edpace.com	Phone: (+44) 1786 460 400 extension	
			J		24461	
			Email: r.kay@medpace.com			



SYNTIMMUNE

02-Mar-2018

Protocol Number:

SYNT001-103

IND Number:

132727

Study Drug:

SYNT001

Protocol Version, Date:

3.0 dated 10-October-2017

Clarification Letter Version: 4.0

Subject:

Sponsor Medical Director

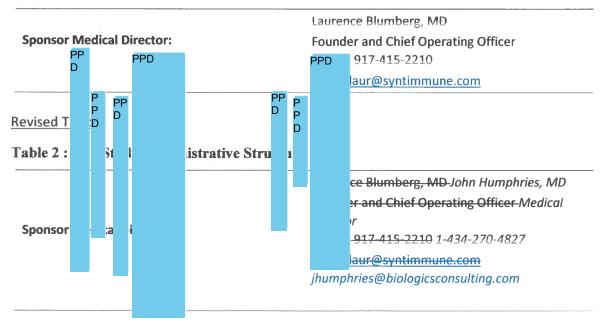
The purpose of this memo is to update the Medical Director details and contact information. Deleted text is crossed through and new text is in italics.

This text will be formally revised in the next forthcoming protocol amendment.

Section 14.1 (page 86)

Current Text:

Table 1: Study Administrative Structure



271 Waverley Oaks Road, Suite 104, Waltham, MA 02452

Page 1 of 2

Sincerely,

Sphanie Valler

Stephanie Haller

Vice President, Clinical Operations

Syntimmune, Inc.

DDD

SYNTIMMUNE, INC. CLINICAL STUDY PROTOCOL

A Phase 1b/2, Multicenter, Open-Label, Safety, and Dose-Finding Study of SYNT001 in Subjects with Pemphigus (Vulgaris or Foliaceus)

Protocol Number: SYNT001-103

IND Number: 132727 Study Drug: SYNT001

Sponsor: Syntimmune, Inc.

116 Huntington Avenue

Suite 301

Boston, MA 02116

Medical Monitor:

Wallace House

17-21 Maxwell Place Stirling, Scotland FK81JU

Mobile Phone: PPD Office Phone: PPD

ext. PPD

Original Protocol:18 January 2017Amendment 1.1:21 March 2017Amendment 2.012 April 2017Amendment 3.010 October 2017Amendment 4.08 June 2018

CONFIDENTIALITY STATEMENT

The information contained herein is confidential and the proprietary property of Syntimmune, Inc. Any unauthorized use or disclosure of such information without the prior written authorization of Syntimmune is expressly prohibited.

SPONSOR SIGNATURE

I have read and approve this protocol. My signature, in conjunction with the signature of the Investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the United States Code of Federal Regulations (CFR), and the ethical principles that have their origins in the Declaration of Helsinki.

PPD	8 JUNE 2018
	Date of Signature
Syntimmune, Inc.	

INVESTIGATOR SIGNATURE

I have read and approve this protocol. My signature, in conjunction with the signature of the Sponsor, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the United States Code of Federal Regulations (CFR), and the ethical principles that have their origins in the Declaration of Helsinki.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care under applicable regulations.		
Investigator Signature	Date of Signature	
Name of Investigator (please print)		

1. SYNOPSIS

Study title	A Phase 1b/2, Multicenter, Open-Label, Safety, and Dose-Finding Study of SYNT001 in Subjects with Pemphigus (Vulgaris or Foliaceus)
Sponsor	Syntimmune, Inc.
Protocol number	SYNT001-103
Clinical phase	Phase 1b/2
Number of study centers	Approximately 10 global study sites
Study rationale	Pemphigus is a potentially life-threatening group of rare blistering autoimmune diseases that affect the skin and mucous membranes. The exact cause is unknown, though autoantibodies are thought to play an important pathogenic role in the mucosal and cutaneous manifestations in patients with pemphigus. The prognosis of pemphigus has markedly improved over the last decades with the prognosis of pemphigus are profiled to a profiled the prognosis of pemphigus has markedly improved over the last decades with
	steroid therapy. Nevertheless, mortality remains an issue (1.6% to 12% of cases) (Hsu et al., 2016; Kasperkiewicz et al., 2017; Langan et al., 2008). In these cases, death typically occurs as a consequence of treatment-related systemic infections and in a smaller proportion, as a consequence of superinfected lesions. While steroids have greatly improved patient outcomes, they are associated with serious and long-lasting side effects; therefore, their use should be limited as much as possible. Although other currently available treatments for certain autoimmune disorders, including immunosuppressants, intravenous immunoglobulin (IVIG), plasmapheresis, and anti-CD20 monoclonal antibodies (mAbs), such as rituximab, can be effective, they can be associated with significant adverse effects and delayed or non-durable responses.
	SYNT001 targets key mechanisms contributing to pathology in a variety of immunoglobulin G (IgG)-mediated autoimmune disorders. When administered to healthy subjects, SYNT001 has been shown to significantly decrease total IgG, as well as immune complexes with which IgG is associated. Based on these results, it is predicted that SYNT001 will also reduce the levels of pathogenic autoantibodies. This could lead to a decrease in the mucosal and cutaneous manifestations in patients with pemphigus. Moreover, the ability of SYNT001 to reduce circulating immune complexes (CICs) and the associated innate and adaptive immune responses may allow for sustained disease modification. Thus, this study is being conducted to evaluate the safety and immunogenicity and determine a minimally effective dose (MED) of intravenous (IV) SYNT001 in pemphigus patients.
Study objectives and endpoints	The study objectives and their corresponding endpoints (primary, secondary, and exploratory) are detailed below.

Primary Objectives	Primary Endpoints
Safety: To evaluate the safety of once-weekly IV infusions of SYNT001 at different dose levels and dosing durations in subjects with pemphigus (vulgaris or foliaceus)	Safety: The evaluation of SYNT001 safety based on vital signs, physical examinations, electrocardiograms (ECGs), clinical safety laboratory tests, the incidence of adverse events (AEs), treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) summarized by cohort, severity, and relationship to study product
Dose Selection: To determine a MED of SYNT001 as assessed by (i) total IgG level nadir and (ii) the proportion of subjects that meet the criteria for response by Pemphigus Disease Area Index total activity score (PDAI)	Dose Selection: The determination of dose and dosing duration of SYNT001 that achieves (i) total IgG level nadir decrease by ≥60% and ≤90% from baseline and (ii) a PDAI total activity score of ≥50% reduction from baseline to allow further clinical development in subjects with pemphigus (vulgaris or foliaceus)
Secondary Objectives	Secondary Endpoints
To determine the pharmacokinetics (PK) of SYNT001 following onceweekly IV infusions at different dose levels and dosing durations	The determination of PK parameters including half-life $(t_{1/2})$, maximum serum concentration determined directly from the concentration-time profile (C_{max}) , observed time of peak plasma concentration (T_{max}) , area under the serum concentration-time curve from pre-dose $(time_0)$ to 24 hours post-dose (AUC_{0-24}) , and area under the serum concentration-time curve from pre-dose $(time_0)$ to infinity $(AUC_{0-\infty})$, $(Cohort\ 1)$; maximum plasma concentration determined directly from the concentration-time profile (C_{max}) and T_{max} $(Cohort\ 2$ onwards) summarized by cohort and timepoint
To evaluate the effect of once- weekly doses of SYNT001 at different dose levels and dosing durations on pharmacodynamics (PD) biomarkers	The evaluation of PD biomarkers based on absolute serum levels and percent change from baseline in serum levels of total immunoglobulin G (IgG), IgG subtypes (IgG1-4), immunoglobulin A (IgA), immunoglobulin M (IgM), albumin, and CIC summarized by cohort and timepoint

T=	
To assess the effect of once-weekly doses of SYNT001 at different dose levels and dosing durations on disease markers	 The assessment of pemphigus disease activity by responses on PDAI based on absolute and percent change from baseline will be summarized by cohort and timepoint. The assessment of pemphigus disease pathogenic antibody levels based on absolute and percent change from baseline of serum anti-desmoglein 1 and 3 antibody (anti-Dsg 1 and anti-Dsg 3) levels that will be summarized by cohort and timepoint
To measure the immunogenicity of once-weekly administered SYNT001 at different dose levels and dosing durations	The immunogenicity of once-weekly administered SYNT001 as determined by presence of anti-SYNT001 binding antibodies and neutralizing antibodies summarized by cohort and timepoint
Exploratory Objectives	Exploratory Endpoints
To explore the effect of once-weekly doses of SYNT001 at different dose levels and dosing durations on biomarkers to understand the pathophysiology of the disease and the SYNT001 mechanisms of action	The exploration of SYNT001 mechanisms of action and effects of SYNT001 on pathophysiology summarized by cohort and timepoint as determined by: Complement component 3 (C3) levels by nephelometry Anti-epithelial cell antibody (AECA) titers by indirect immunofluorescence Fc gamma R2A receptor (FCGR2A) single nucleotide polymorphisms (SNP) by genotyping Presence of disease and inflammatory markers by RNAseq (RNA sequencing) Immunophenotyping via measures of T cells, monocytes, NK cells and B cells by flow cytometry Urine IgG levels to explore SYNT001 distribution and elimination Exploratory biomarkers to investigate immune response associated with pemphigus

	To determine the impact of different SYNT001 dose levels and dosing durations on the subject's use of corticosteroids to treat their pemphigus (vulgaris or foliaceus) To assess the impact of once-weekly doses of SYNT001 on the subject's health-related quality of life (HR-QoL) at different dose levels and dosing durations	The evaluation of corticosteroid use during the study will be summarized by cohort and timepoint The assessment of SYNT001 impact on subject's health-related quality of life (HR-QoL) by responses to the Autoimmune Bullous Diseases Quality of Life (ABQoL) questionnaire and Skindex-29 scores summarized by cohort and timepoint	
	To assess the effect of once-weekly doses of SYNT001 on the appearance of skin and mucosal lesions at different dose levels and dosing durations	The qualitative assessment of changes in appearance of skin and mucosal lesions as determined by photography presented by cohort and timepoint	
	To quantify the amount of SYNT001 in skin (skin biopsies optional)	The determination of SYNT001 levels in skin biopsies across timepoints (skin biopsies optional)	
Study design	This is a multicenter, open-label safety study to determine the dose regimen of SYNT001 administered intravenously in subjects with pemphigus (vulgaris or foliaceus). Approximately 20 (up to a maximum of 32) eligible subjects with a diagnosis of active pemphigus vulgaris or pemphigus foliaceus will receive planned doses of 10 mg/kg up to 45 mg/kg of SYNT001. Eligible subjects will be enrolled in Cohort 1 and then sequential cohorts, pending recommendation received from the scheduled Dose Escalation Committee (DEC) review. The DEC will consist of the Medical Monitor, an Independent Clinical Expert and a Syntimmune Medical Officer. To assist in the safety assessments, the DEC may request that Investigators, other experts, or members within their organization review the data and participate in the discussions. Each cohort must be fully enrolled before a successive cohort will be opened for enrollment. Cohort 4 is optional and will be added at the discretion of the sponsor and/or DEC. An overview of the study cohorts is provided in Table 1 and Figure 1 shows a schematic of the study design.		

Table 1.	Cohort	Overview		
Cohort No.	No. of Subjects	SYNT001 Dose	No. of Doses	DEC Review Timepoint
1 ^a	up to 8	10 mg/kg	5	NA
2 ^b	4°	≤30 mg/kg ^d	5	When 100% of Cohort 1 subjects reach Day 42
3 ^b	4 ^c	≤30 mg/kg ^d	14	When 50% of Cohort 2 subjects reach Day 42
4 ^b (optional)	4 ^c	≤45 mg/kg ^d	≤14	When 50% of Cohort 3 subjects reach Day 42°

Abbreviations: DEC = Dose Escalation Committee; NA = not applicable

- a. No more than 3 subjects with pemphigus foliaceus may be enrolled
- b. Two or fewer subjects with pemphigus foliaceus may be enrolled
- c. Up to 4 additional subjects may be added following DEC's evaluation.
- d. Dose will be recommended by the DEC and will be based on both an ongoing and set timepoint review of safety and pharmacodynamic evaluations including but not limited to, dose-limiting toxicities (DLTs), adverse events (AEs), treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and total IgG levels.
- e. All available data will be considered.

The first 2 subjects in Cohorts 1 and 2 will be enrolled at staggered intervals to facilitate adequate safety evaluation before dosing of subsequent subjects may proceed. A staggered dosing interval for the first 2 subjects enrolled in successive cohorts will not be required if the planned dose is equal to or lower than that previously administered.

At 24-hour and 7-day intervals described below, the DEC will review all available safety data (including but not limited to dose limiting toxicities [DLTs], AEs, TEAEs, and SAEs, PD (including but not limited to total IgG levels), and clinical outcomes.

DEC Safety Review of 24-hour Data for Cohorts 1 and 2, Subject 1

• The first 2 subjects will be dosed at least 24 hours apart. A DEC review of the 24-hour safety data for the first subject will be performed to ensure that there are no overt safety concerns before dosing the second subject.

DEC Safety Review of 7-day Data for Cohorts 1 and 2, Subjects 1 and 2

• The 7-day safety data for the first 2 subjects will be performed prior to dosing the remaining subjects in the cohort.

The 24-hour and 7-day reviews will consider seriousness and severity of AEs/TEAEs/SAEs and relatedness to study drug, vital sign assessments, physical examinations, and clinical laboratory testing.

At scheduled reviews, the DEC may recommend increasing the number of subjects to be enrolled (from 4 up to 8 as shown in Table 1) and advise on the planned dose for each successive cohort. Further, the DEC may recommend pausing and resuming or halting enrollment.

Further, at any time during the study, the DEC may review all available safety data (including but not limited to DLTs, AEs, TEAEs, and SAEs), PD (including but not limited to IgG levels), and clinical outcomes.

- If 2 or more subjects at any time in any cohort have Grade 3 AEs that are determined to be clinically significant and considered to be related to study drug, dosing will be halted within that cohort and dose-escalation to a higher dose will not occur. Upon review of the available information, the DEC may reduce the dose prior to enrolling additional subjects using the guidelines below:
 - Cohort 1: Dose may be reduced by at least 50%.
 - Cohort 2: Dose may be reduced by at least 33%.
 - Cohort 3: Dose may be reduced to a level lower than the Cohort 2 dose.
 - Cohort 4 (optional cohort): Dose may be reduced to level lower than the Cohort 3 dose.

NOTE: DLT will be defined generally as severe (Grade 3) AEs occurring in ≥2 subjects that are determined to be clinically significant and considered related to study drug.

- If any subject at any time during the study experiences a life-threatening AE (Grade 4) that is related to study drug, further dosing in all enrolled subjects will be suspended until the DEC has evaluated the event and determined the appropriate course of action.
- At any time during the study, the study or any ongoing study cohort may be discontinued if the DEC determines that further drug exposure would pose an undue risk to subjects.

Additional information on the DEC's responsibilities as they pertain to data review, dose selection, opening and closing a cohort, individual and study stopping recommendations is provided in Section 9 and the DEC charter.

Study methodology

Study participation requires that the subject will have completed the following periods of assessment to be performed on a weekly basis: Screening, Treatment (Baseline [Day 0], Major and Minor Dosing Visit days), and a Follow-Up (Major and Minor Visit days).

Throughout the study, during each period of assessment to evaluate safety and tolerability, subjects will undergo physical examinations (including weight), vital sign measurements (including pulse oximetry), clinical (safety) laboratory tests, AEs, concomitant medication assessments, and ECGs.

Screening Period (up to 14 days)

After the subject has provided written informed consent, the Investigator or other qualified study personnel will determine if the subject is eligible for the study. This will be accomplished by reviewing the inclusion and exclusion criteria, and the subject's demographic profile, screening PDAI total activity score, and medical history.

Treatment Period (28 or 91 days)

The treatment period includes the Baseline (Day 0) Dosing Visit day, and Major and Minor Dosing Visit days. Refer to Table 2, Table 3, Table 4, and Section 7.

Baseline (Day 0) Visit Day

In addition to the safety and tolerability assessments described above, the subject will be administered the study drug and the following procedures will be conducted: pregnancy test (if applicable), PDAI, PK, PD, and immunogenicity sample collection, photography of lesions, and serum tetanus and varicella zoster virus (VZV) antibody tests. An optional skin biopsy may be collected. HR-QoL is assessed in all cohorts except Cohort 1. A complete list of assessments is provided in Table 2, Table 3, Table 4, and Section 7.

Major Dosing Visit Days

In addition to the safety and tolerability assessments described above, the subject will be administered the study drug, and the following procedures will be conducted: PDAI, PD, and immunogenicity sample collection. A complete list of assessments is provided in Table 2, Table 3, Table 4, and Section 7.

Minor Dosing Visit Days

In addition to the safety and tolerability assessments described above, the subject will be administered the study drug, and the following procedures will be conducted: PDAI and PD sample collection. A complete list of assessments is provided in Table 2, Table 3, Table 4, and Section 7.

Follow-up Period/End of Study (84 days)

The follow-up period includes the Major and Minor Follow-up Visit days. Subjects are encouraged to participate in all visits up to and including Day 112 (Cohorts 1 and 2) or Day 175 (Cohort 3) to ensure study completion. Refer to Table 2, Table 3, Table 4, and Section 7.

Major Follow-up Visit Days

In addition to the safety and tolerability assessments described above, the following procedures will be conducted: PDAI, PD sample collection, photography of lesions and HR-QoL assessments. A complete list of assessments is provided in Table 2, Table 3, Table 4, and Section 7.

Minor Follow-up Visit Days

In addition to the safety and tolerability assessments described above, the following procedures will be conducted: PDAI and PD sample collection. A complete list of assessments is provided in Table 2, Table 3, Table 4, and Section 7.

Dosing for any individual subject will be discontinued (ie, further treatment with the study drug will not be given) if the subject experiences any study drug-related SAE or any study drug-related non-serious adverse event that, in the judgement of the Investigator (following consultation with the Medical Monitor, if desired) suggests that it could be unsafe to administer further study drug to that subject. Additionally, a subject will be discontinued from further treatment with study drug at the discretion of the Investigator, with consultation with the Medical Monitor if desired, if they require a significant increase in anti-pemphigus medications for the management of pemphigus.

G. 1			
Study population	Male or female subjects aged 18 and older with pemphigus (vulgaris or		
Inclusion criteria	foliaceus) in active stage Subjects must meet the following criterie to be included:		
inclusion criteria	Subjects must meet the following criteria to be included:		
	1. Willing and able to read, understand, and sign an informed consent form.		
	 Male or female ≥18 years of age at the time of screening. Documented diagnosis of pemphigus vulgaris or foliaceus based on all 3 		
	of the following criteria:		
	a. Documented clinical history consistent with pemphigus vulgaris or		
	foliaceus (clinical presentation defined as mucosal and/or skin lesions).		
	b. Presence of Anti-Dsg 1 or 3 antibodies above the upper limit of normal (ULN).		
	c. History of at least one positive tissue-based test (eg, biopsy, direct immunofluorescence [DIF]).		
	4. Active disease defined as lesions lasting >2 weeks, and 3 active lesions in		
	skin or mucosa or 2 active lesions with at least one being a skin lesion		
	>1 cm diameter:		
	a. If treated with rituximab or other anti-CD20 mAb, last dose >12 months prior to screening.		
	b. If being treated with other immunosuppressants (ie, azathioprine,		
	mycophenolate mofetil, methotrexate, dapsone, cyclosporine,		
	tacrolimus, sirolimus, or low-dose cyclophosphamide		
	[\le 100 mg/day]), dose must be stable, defined as <25% change in		
	dose, for 4 weeks prior to screening.		
	c. On stable dose of corticosteroids, defined as ≤1 mg/kg of		
	prednisone or equivalent and may not be increased by more than		
	50% in the 2 weeks prior to screening.		
	d. Allowed topical therapies for pemphigus lesions upon entering the study include petroleum jelly or Aquaphor® for the skin or chlorhexidine for the mouth.		
	e. Stable use of topical low strength hydrocortisone (≤1%),		
	tacrolimus, sirolimus, or pimecrolimus for lesions contributing		
	<10% of the PDAI total activity score for the 4 weeks prior to		
	screening is allowed. Stable use of dexamethasone elixir solution		
	(swish and spit only) for oral lesions for the 4 weeks prior to		
	screening is allowed.		
	f. If not on regular corticosteroids, no pulse corticosteroids are		
	allowed in the 2 weeks prior to screening.		
	 5. Body mass index (BMI) >18.5 kg/m². 6. Has a negative pregnancy test documented prior to the first dose of study 		
	drug (for women of childbearing potential).		
	7. Females of childbearing potential must agree to be abstinent or else use		
	any two of the following medically acceptable forms of contraception		
	(<1% per year failure rate) from the screening period through the final		
	study visit: oral contraceptive, condom with or without spermicidal jelly,		
	diaphragm or cervical cap with spermicidal jelly, or intrauterine device		
	(IUD). A female whose male partner has had a vasectomy must agree to		
	use one additional form of medically acceptable contraception.		

r	,
	8. Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or
	post-menopausal for at least 12 months do not require contraception
	during the study.
	9. Males with female partners of childbearing potential, including males who
	are surgically sterile (post vasectomy), must agree to be abstinent or else
	use a medically acceptable form of contraception from the screening
	period through 60 days after the final study visit.
7	10. A PDAI total activity score of >4 at screening.
Exclusion criteria	Subjects meeting any of the following criteria are to be excluded:
	1. Subject unable or unwilling to comply with the protocol.
	2. Active non-hematologic malignancy or history of non-hematologic
	malignancy in the 3 years prior to screening (exclusive of non-melanoma
	skin cancer and cervical cancer in situ). 3. Positive for human immunodeficiency virus (HIV) or hepatitis C antibody.
	4. Positive for hepatitis B surface antigen.
	5. Active infection or history of recurrent infections.
	6. IVIG treatment within 30 days of screening.
	7. Received any cytotoxic (other than azathioprine) or any non-anti-CD20
	mAb therapy in the 3 months prior to screening.
	8. Any exposure to an investigational drug or device within the 30 days prior to screening.
	9. Plasmapheresis or immunoadsorption within 30 days of screening.
	10. Cellular therapy, including chimeric antigen receptor and T-cell (CAR-T), at any time prior to screening.
	11. Use of any systemic or topical immunosuppressive drugs within 3 months
	of screening not including dose allowed by the inclusion criteria.
	12. Serum total IgG <600 mg/dL.
	13. Subject has any current medical condition that, in the opinion of the
	Investigator, may compromise their safety or compliance, preclude
	successful conduct of the study, or interfere with interpretation of the results (eg, a significant pre-existing illness or other major comorbidity
	that the Investigator considers may confound the interpretation of the
	study results).
	14. Any vaccination within 2 weeks of screening.
Study drug, dosage,	Study drug: SYNT001
and administration	Dosage:
	Cohort 1: 10 mg/kg, 5 weekly IV doses
	Cohort 2: ≤30 mg/kg, 5 weekly IV doses
	Cohort 3: ≤30 mg/kg, 14 weekly IV doses
	Cohort 4 (optional cohort): ≤45 mg/kg, ≤14 weekly IV doses
	Product presentation and preparation:
	SYNT001 provided as a liquid at a nominal concentration of 50 mg/mL. SYNT001 is diluted in dextrose 5% in water (D5W) to prepare the solution for infusion.
	Route of administration: IV in 250 mL over 1 hour ± 15 minutes
	Noute of authinistration: 1 v III 250 IIIL over 1 hour ± 15 minutes

Control, dose, and	Not applical	ole									
route of administration											
Duration of subject	The duration	n of subject no	articipation fo	r each cohort	is as follow	c·					
participation	Cohorta	Screening	Treatment	Follow-up	Maximum						
	Conort	Sercening	Treatment	1 onow up	Days	Weeks					
	1	≤14 days	28 days	84 days	126 days	18 weeks					
	2	≤14 days	28 days	84 days	126 days	18 weeks					
	3	≤14 days	91 days	84 days	189 days	27 weeks					
				•	,	al cohort) will be					
			EC data review.								
Permitted and		•	eceives within	• •	or to enrollm	ent through					
prohibited	the end of the study will be documented.										
concomitant treatments		Medications									
treatments			and treatment		_	s, including					
	1	those for pemphigus, are permitted if not listed as prohibited.									
		1. Topical antibiotics to treat active infections that occur during the study.									
	_	 Topical or systemic treatments for oral candidiasis. Topical lidocaine for transient pain relief as needed. 									
						Es the subject					
		nces during th			- u 101 uni j 11.	as are suejeer					
	5. Medicat	ion for potent	ial infusion re	eactions: The	Investigator	may					
			ctic use of ace								
	-	•	, ,	. •	ranitidine, fa	amotidine), etc					
			nfusion reaction		e <1%) annli	ed to a single					
			.0% of the PD			ed to a single					
	7. Topical	tacrolimus, si	rolimus or pir the PDAI total	mecrolimus a	pplied to a s	ingle lesion					
		-	solution for o	•		ıs stable					
			ipation (swisl			15 544615					
			following sys								
						, cyclosporine,					
						(100 mg/day).					
			on. Prohibite			be tapered at					
						e study unless					
		ove as permit		iot de perimi	ica during in	e study unless					
			ti-CD20 antil	•							
			es other than s								
		ical or system d as permitted	ic immunosu	ppressive dru	igs apart froi	n those that					
		-	or to infusion	(except in su	biects who r	eceived					
			atment of a pr								
		tary herbal su			2	- /					
	6. Any inv	estigational d	rug or device								
			weeks of scr	eening throu	gh 28 days fo	ollowing final					
	dose of	study drug									

Statistical considerations

Three populations will be employed in the analysis of study data:

- The safety population will consist of all subjects who have received at least one dose of study drug.
- The PD population will consist of all subjects who receive at least one dose of study drug and have post-dose PD data available.
- The PK population will consist of all subjects who receive at least one dose of study drug and have post-dose PK data available.

Primary safety analyses will be performed on the safety population. Demographics, subject disposition, screening, and baseline characteristics will be summarized for the safety and PD/PK populations, where appropriate.

Sample size

Formal sample size calculations were not performed. The number of subjects was chosen based on feasibility and was considered sufficient to meet the study objectives.

Criteria for evaluation

Baseline analysis

Baseline characteristics to include medical history, physical examination, vital signs, and ECG will be summarized using descriptive statistics by cohort.

Safety analysis

The evaluation of SYNT001 based on vital signs, physical examination, ECGs, clinical safety laboratory tests, the incidence of AEs, TEAEs, and SAEs summarized by cohort, severity, and relationship to study product.

Dose-finding analysis

The evaluation of SYNT001 based on total IgG levels and responses on the PDAI total activity score from baseline will be summarized using descriptive statistics by cohort.

Statistical methodology

Treatment-emergent AEs (TEAEs) will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA®; Version 19 or higher) System Organ Class (SOC) and preferred term, classified from verbatim terms. The incidence and percentage of subjects with at least one occurrence of a preferred term will be included, using the most severe grade. The number of events per preferred term will also be summarized. Causality (relationship to study treatment) will be summarized separately.

TEAEs, SAEs, and AEs leading to withdrawal, dose modification, or treatment discontinuation will be listed by subject and dose using SOC and preferred terms. Duration of AEs will be determined and included in listings, along with action taken and outcome.

Laboratory results will be summarized by time point and cohort. The incidence of laboratory abnormalities will be summarized. The worst on-study grade

after the first dose of study drug will be summarized. Results for variables that are not coded will be presented in the listings as below, within, or above the normal limits of the central laboratory. Vital sign measurements will be summarized by cohort at each scheduled time point using descriptive statistics. PD/PK results will be summarized by cohort. Descriptive statistics of PD/PK parameters for SYNT001 will include mean, standard deviation (SD), coefficient of variation (CV), median, minimum, and maximum Immunogenicity results will be summarized by cohort and timepoint. Descriptive statistics will include mean, SD, median, minimum, and maximum.

PDAI results will be summarized by score (total activity score, total damage score), cohort, and timepoint. Descriptive statistics will include absolute change from baseline and percent change from baseline.

Figure 1. Cohort Enrollment

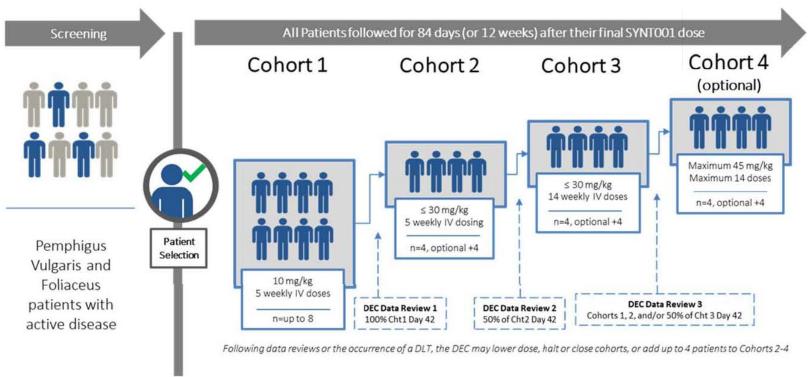


Table 2. Study Assessments for Cohort 1

	Screening							Tre	atment	Period							Follo	w-Up
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Time point (study day)	-14 to -1	0	1	2	5 ^p	7	12 ^p	14	19 ^p	21	28	29	30	33	42	56	84	112 or
			(±1 h)	(±2 h)	(±4 h)	(±6 h)	(±6 h)	(±6 h)	(±6 h)	(±6 h)	(±6 h)	(±1 h)	(±2 h)	(±4 h)	(±3 d)	(±5 d)	(±5 d)	ET (±5 d)
Informed consent	X																	
Demographics/medical history	X																	
Inclusion/exclusion	X																	
Physical examination ^a	X	X				X		X		X	X				X	X	X	X
Vital signs ^b	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pulse oximetry ^c		X				X		X		X	X							
Clinical safety labs ^d	X	X				X		X		X	X			X	X	X	X	X
Pregnancy test ^e	X	X														X		X
Hepatitis and HIV screen	X																	
12-lead ECG ^f	X	X					X				X					X		
Tetanus and VZV antibodies ^g		X														X	X	X
PDAI		X				X		X		X	X			X	X	X	X	X
PK sampling ^h		X	X	X	X						X	X	X	X				
Immunogenicity ⁱ		X						X			X					X	X	X
Study drug administration ^j		X				X		X		X	X							
Immunoglobulins (IgG, IgA, IgM) and IgG subtypes (IgG1-4) ^k	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Xq
CIC		X			X	X	X	X	X	X	X			X	X	X	X	X
Anti-Dsg (1 and 3) antibody titers	X	X				X		X						X		X	X	X
C3 and AECA ¹		X						X						X		X	X	X
FCGR2A by buccal swab ^m		X																
RNAseq		X						X						X		X	X	X
Urine IgG		X						X						X		X	X	X
Immunophenotyping ⁿ		X									X					X		
Exploratory pemphigus immune response biomarkers		X			X	X	X	X	X	X	X			X	X	X	X	X
Optional skin biopsy		X	X	X				X						X		X	X	
Photography ^o		X												X		X	X	X
Adverse events					To be c	ollected	from the	e date th	at the IC	CF is sig	ned thro	ugh the	last stud	ly visit				
Concomitant medications							from wi											

Abbreviations: CIC = circulating immune complexes; d = days; ECG = electrocardiogram; ET = early termination; h = hour(s); HIV = human immunodeficiency virus; ICF = informed consent form; PDAI = Pemphigus Disease Area Index; PK = pharmacokinetic; VZV = varicella zoster virus.

- a. Complete physical examination, including weight, to be performed. Height and BMI will be additional assessments conducted at screening.
- b. **Vital sign** measurements (sitting blood pressure, heart rate, respiratory rate, and oral temperature) to be obtained after 5 minutes of seated rest. Any abnormal measurements are to be repeated after 5 minutes of rest. On Days 0, 7, 14, 21, and 28, vital sign measurements will be collected immediately prior to the infusion; 15, 30, and 45 minutes after the start of the infusion; at completion of the infusion; and 30 minutes, 1 hour, and 2 hours following completion of the infusion.
- c. **Pulse oximetry:** On Days 0, 7, 14, 21, and 28, pulse oximetry to be measured immediately prior to the infusion; 15, 30, and 45 minutes after the start of the infusion; at completion of the infusion; and 30 minutes, 1 hour and 2 hours following completion of the infusion.
- d. Clinical safety labs: hematology, clinical chemistry, and urinalysis (see Section 7.5 for a complete list). Full clinical safety laboratory draws will be collected at screening and on Days 0, 7, 14, 21, 28, 33, 42, 56, 84, and 112.
- e. **Pregnancy test**: To be performed at time of screening, prior to first dose of SYNT001 on Day 0, and on Days 56 and 112. Urine or serum test is acceptable; however, positive urine tests must be confirmed with serum testing.
- f. Digital 12-lead ECG to be obtained in triplicate at least 1 to 2 minutes apart and after 5 minutes of rest in a supine position. See Section 7.6 for additional information. On Days 0 and 28 to be obtained 5 minutes after the completion of infusion. Day 12 ECG will be collected only if the visit is conducted at the study site.
- g. **Serology**: Testing at Day 56 will not be done for any subject whose baseline titer is below the level of detection. If the Day 56 results are greater than 30% below the baseline value, or if the subject falls below the level of detection, the subject will be re-tested at Day 84; if still below the baseline value (or level of detection), the subject will be re-tested at Day 112. Any subject whose baseline value for tetanus or VZV was above the detectable level at baseline, and is not within 30% of the baseline value or is below the detectable level by Day 112, will be referred to their primary care physician for further management. See Section 7.5.3 for additional information.
- h. **PK**: Starting on Days 0 and 28, serum samples will be collected just prior to the start of study drug infusion (pre-dose), and at 5 minutes and 2, 4, 6, 24, and 48 hours after the end-of-study drug infusion. Additional samples will be collected on Days 5 and 33. See Section 7.5.4 for additional information.
- i. Immunogenicity: Samples will be collected pre-dose when collected on dosing days. Samples will be collected on Days 0, 14, 28, 56, 84 and 112. See Section 7.5.6 for additional information.
- j. Prior to **study drug infusion**, SYNT001 drug product is to be diluted in dextrose 5% in water (D5W) to a total volume of 250 mL and administered intravenously over 1 hour using a 0.2-micron inline filter. See Section 4 and Section 7.8 for additional information.
- k. Immunoglobulins (IgG, IgA, IgM) and IgG subtypes (IgG1-4): Collected for measurements of IgG, IgG subtypes (IgG1-4), IgA, IgM at every visit. On Days 0, 7, 14, 21, and 28, samples are collected prior to infusion of study drug. See Section 7.5.5 for additional information.
- 1. **Exploratory pharmacodynamic samples (C3 and AECA):** Collected pre-dose when collected on dosing days. See Section 7.5.5 for complete information.
- m. Buccal samples to be collected and stored; pending review of clinical and pharmacodynamics assessments.
- n. Immunophenotyping by flow cytometry for measurement of CD3⁺CD4⁺ T, CD3⁺CD8⁺ T, monocytes, NK cells and B cells.
- o. Photographs of active lesions taken prior to first dose on Day 0. Follow-up photographs will be taken at Days 33, 56, 84 and 112. Subjects who begin a steroid taper will have additional photographs taken at the clinic visit during which the decision to begin the taper is made.
- p. Visit Days 5, 12, and 19 may be conducted via at-home nurse in lieu of a subject visit to the study site.
- q. Subjects will return to the clinic on Days 84 and 112 for follow-up visits. Subjects whose total IgG is not within 30% of their Day 0 baseline value and not above 500 mg/dL at the Day 112 visit will be referred for further management.

Table 3. Study Assessments for Cohort 2

	Screening		Tr	eatment Per	iod				Follow-Up		
Visit number	1	2	3	4	5	6	7	8	9	10	11
Time point (study day)	-14 to -1	0	7 (±1 d)	14 (±1 d)	21 (±1 d)	28 (±1 d)	35 (±1 d)	42 (±1 d)	56 (±3 d)	84 (±5 d)	112 or ET (±5 d)
Informed consent	X										
Demographics/medical history	X										
Inclusion/exclusion	X										
Physical examination ^a	X	X	X	X	X	X	X	X	X	X	X
Vital signs ^b	X	X	X	X	X	X	X	X	X	X	X
Pulse oximetry ^c		X	X	X	X	X					
Clinical safety labs ^d	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test ^e	X	X							X		X
Hepatitis and HIV screen	X										
12-lead ECG ^f	X	X		X		X			X		
Tetanus and VZV antibodies ^g		X							X		X
PDAI ^h	X	X	X	X	X	X	X	X	X	X	X
PK sampling ⁱ		X				X					
Immunogenicity ^j		X		X		X			X		X
Study drug administration ^k		X	X	X	X	X					
Immunoglobulins (IgG, IgA, IgM) and IgG subtypes (IgG1-4) ¹	X	X	X	X	X	X	X	X	X	X	X^q
CIC		X	X	X	X	X	X	X	X	X	X
Anti-Dsg (1 and 3) antibody titers	X	X	X	X	X	X	X	X	X	X	X
C3 and AECA ^m		X					X		X		
FCGR2A by buccal swab ⁿ		X									
RNAseq		X					X		X		
Urine IgG		X					X		X		
Immunophenotyping ^o		X					X		X		
Exploratory pemphigus immune response biomarkers		X	X	X	X	X	X	X	X	X	X
Photography ^p		X X					X		X		X
HR-QoL assessments		X					X		X		X
Adverse events		-	To be	collected from	n the date the	at the ICF is s	igned throug	h the last stu	dy visit		
Concomitant medications			To be	collected from	n within 14 a	lays prior to l	Day 0 through	h th <mark>e last stud</mark>	ly visit		

Abbreviations: CIC = circulating immune complexes; d = day(s); ECG = electrocardiogram; ET = early termination; HIV = human immunodeficiency virus; HR-QoL = health-related quality of life; ICF = informed consent form; PDAI = Pemphigus Disease Area Index; PK = pharmacokinetic; VZV = varicella zoster virus.

a. Complete physical examination, including weight, to be performed. Height and BMI will be additional assessments conducted at screening.

b. **Vital sign** measurements (sitting blood pressure, heart rate, respiratory rate, and oral temperature) to be obtained after 5 minutes of seated rest. Any abnormal measurements are to be repeated after 5 minutes of rest. Vital sign measurements will be taken on all study visits. On Days 0, 7, 14, 21, and 28, vital sign measurements

- will be collected immediately prior to the infusion; 15, 30, and 45 minutes after the start of the infusion; at completion of the infusion; and 30 minutes, 1 hour, and 2 hours following completion of the infusion.
- c. **Pulse oximetry:** On Days 0, 7, 14, 21, and 28, pulse oximetry to be measured immediately prior to the infusion; 15, 30, and 45 minutes after the start of the infusion; at completion of the infusion; and 30 minutes, 1 hour and 2 hours following completion of the infusion.
- d. Clinical safety labs: hematology, clinical chemistry, and urinalysis (see Section 7.5 for a complete list). Full clinical safety laboratory draws will be collected at screening and on all study visits.
- e. **Pregnancy test**: To be performed at time of screening, prior to first dose of SYNT001 on Day 0, and on Days 56 and 112. Urine or serum test is acceptable; however, positive urine tests must be confirmed with serum testing.
- f. Digital 12-lead ECG to be obtained in triplicate at least 1 to 2 minutes apart and after 5 minutes of rest in a supine position. See Section 7.6 for additional information. On treatment days to be obtained 5 minutes after the completion of infusion.
- g. **Serology**: Any subject whose baseline value for tetanus or VZV was above the detectable level at baseline and is not within 30% of the baseline value or is below the protective level by End of Treatment will be referred to their primary care physician for further management. See Section 7.5.3 for additional information.
- h. **PDAI** will be administered at screening. Subject eligibility requires a PDAI total activity score >4. Thereafter, assuming eligibility, the PDAI will be administered during Treatment Period and Follow-up Period. See Section 7.7 for additional information.
- i. **PK**: On Days 0 and 28, serum samples will be collected just prior to the start of study drug infusion (pre-dose), and at 5 minutes, 1 and 2 hours after the end of study drug infusion. See Section 7.5.4 for additional information.
- j. **Immunogenicity**: Samples will be collected pre-dose when collected on dosing days. Samples will be collected on Days 0, 14, 28, 56, and 112. See Section 7.5.6 for additional information.
- k. Prior to **study drug infusion**, SYNT001 drug product is to be diluted in dextrose 5% in water (D5W) to a total volume of 250 mL and administered intravenously over 1 hour ± 15 minutes using a 0.2-micron inline filter. See Section 4 and Section 7.8 for additional information.
- 1. **Immunoglobulins (IgG, IgA, IgM) and IgG subtypes (IgG1-4):** Collected for measurements of IgG, IgG subtypes (IgG1-4), IgA, IgM at every visit. On Days 0, 7, 14, 21, and 28, samples are collected prior to infusion of study drug. See Section 7.5.5 for additional information.
- m. Exploratory pharmacodynamic samples (C3 and AECA): Collected pre-dose when collected on dosing days. See Section 7.5.5 for complete information.
- n. Buccal samples to be collected and stored; pending review of clinical and pharmacodynamics assessments.
- o. Immunophenotyping by flow cytometry for measurement of CD3⁺CD4⁺ T, CD3⁺CD8⁺ T, monocytes, NK cells and B cells.
- p. Photographs of active lesions taken prior to first dose on Day 0. Follow-up photographs will be taken at Days 35, 56, and 112. Subjects who begin a steroid taper will have additional photographs taken at the clinic visit during which the decision to begin the taper is made.
- q. Subjects will return to the clinic on Days 84 and 112 for follow-up visits. Subjects whose total IgG is not within 30% of their Day 0 baseline value and not above 500 mg/dL at the Day 112 visit will be referred for further management.

Table 4.Study Assessments for Cohort 3

	Screening						,	Treatm	ent Per	iod							F	ollow-U	^J p	
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Time point (study day)	-14 to -1	0	7 (±1 d)	14 (±1 d)	21 (±1 d)	28 (±1 d)	35 (±1 d)	42 (±1 d)	49 (±1 d)	56 (±1 d)	63 (±1 d)	70 (±1 d)	77 (±1 d)	84 (±1 d)	91 (±1 d)	98 (±1 d)	105 (±1 d)	119 (±3 d)	147 (±5 d)	175 or ET (±5 d)
Informed consent	X																			
Demographics/medical history	X																			
Inclusion/exclusion	X																			
Physical examination ^a	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs ^b	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pulse oximetry ^c		X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Clinical safety labs ^d	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test ^e	X	X						X							X			X		X
Hepatitis and HIV screen	X																			
12-lead ECG ^f	X	X						X							X			X		
Tetanus and VZV antibodies ^g		X																X		X
PDAI ^h	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK sampling ⁱ		X													X					
Immunogenicity ^j		X						X							X			X		X
Study drug administrationk		X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Immunoglobulins ^l	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X^q
CIC		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-Dsg (1 and 3) antibody titers	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C3 and AECA ^m		X														X		X		
FCGR2A by buccal swab ⁿ		X																		
RNAseq		X														X		X		
Urine IgG		X														X		X		
Immunophenotyping ^o		X														X		X		
Exploratory pemphigus immune response biomarkers		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Photography ^p		X						X								X		X		X
HR-QoL assessments		X														X		X		X
Adverse events					7	o be co	llected t	rom the	date th	at the IC	CF is sig	ned thr	ough the	e last sti	udy visit					
Concomitant medications															ıdy visit					

Abbreviations: CIC = circulating immune complexes; d = days; ECG = electrocardiogram; ET = early termination; HIV = human immunodeficiency virus; ICF = informed consent form; PDAI = Pemphigus Disease Area Index; PK = pharmacokinetic; VZV = varicella zoster virus.

a. Complete physical examination, including weight, to be performed. Height and BMI will be additional assessments conducted at screening.

b. Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, and oral temperature) to be obtained after 5 minutes of seated rest. Any abnormal measurements are to be repeated after 5 minutes of rest. Vital sign measurements will be taken on all study visits. On Days 0, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84,

- and 91, vital sign measurements will be collected immediately prior to the infusion; 15, 30, and 45 minutes after the start of the infusion; at completion of the infusion; and 30 minutes, 1 hour, and 2 hours following completion of the infusion.
- c. **Pulse oximetry:** On Days 0, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, and 91, pulse oximetry to be measured immediately prior to the infusion; 15, 30, and 45 minutes after the start of the infusion; at completion of the infusion; and 30 minutes, 1 hour and 2 hours following completion of the infusion.
- d. Clinical safety labs: hematology, clinical chemistry, and urinalysis (see Section 7.5 for a complete list). Full clinical safety laboratory draws will be collected at screening and on all study visits.
- e. **Pregnancy test**: To be performed at time of screening, prior to dosing of SYNT001 on Days 0, 42, and 91, and on Days 119 and 175. Urine or serum test is acceptable; however, positive urine tests must be confirmed with serum testing.
- f. Digital 12-lead ECG to be obtained in triplicate at least 1 to 2 minutes apart and after 5 minutes of rest in a supine position. See Section 7.6 for additional information. On treatment days to be obtained 5 minutes after the completion of infusion.
- g. **Serology**: Any subject whose baseline value for tetanus or VZV was above the detectable level at baseline, and is not within 30% of the baseline value or is below the protective level by End of Treatment will be referred to their primary care physician for further management. See Section 7.5.3 for additional information.
- h. **PDAI** will be administered at screening. Subject eligibility requires a PDAI total activity score >4. Thereafter, assuming eligibility, the PDAI will be administered during Treatment Period and Follow-up Period. See Section 7.7 for additional information.
- i. **PK**: Starting on Days 0 and 91, serum samples will be collected just prior to the start of study drug infusion (pre-dose), and at 5 minutes, 1 hour and 2 hours after the end of study drug infusion. Section 7.5.4 for additional information.
- j. Immunogenicity: Samples will be collected pre-dose when collected on dosing days. Samples will be collected on Days 0, 42, 91, 119 and 175. See Section 7.5.6 for additional information.
- k. Prior to **study drug infusion**, SYNT001 drug product is to be diluted in dextrose 5% in water (D5W) to a total volume of 250 mL and administered intravenously over 1 hour ± 15 minutes using a 0.2-micron inline filter. See Section 4 and Section 7.8 for additional information.
- 1. **Immunoglobulins (IgG, IgA, IgM) and IgG subtypes (IgG1-4):** Collected for measurements of IgG, IgG subtypes (IgG1-4), IgA, IgM at every visit. On Days 0, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, and 91, samples are collected prior to infusion of study drug. See Section 7.5.5 for additional information.
- m. Exploratory pharmacodynamic samples (C3 and AECA): Collected pre-dose when collected on dosing days. See Section 7.5.5 for complete information.
- n. Buccal samples to be collected and stored; pending review of clinical and pharmacodynamics assessments.
- o. Immunophenotyping by flow cytometry for measurement of CD3⁺CD4⁺ T, CD3⁺CD8⁺ T, monocytes, NK cells and B cells.
- p. Photographs of active lesions taken prior to first dose on Day 0. Follow-up photographs will be taken at Days 42, 98, 119, and 175. Subjects who begin a steroid taper will have additional photographs taken at the clinic visit during which the decision to begin the taper is made.
- q. Subjects will return to the clinic on Days 147 and 175 for follow-up visits. Subjects whose total IgG is not within 30% of their Day 0 baseline value and not above 500 mg/dL at the Day 175 visit will be referred for further management.

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LIST OF ABBREVIATIONS

Autoimmune Bullous Disease Quality of Life **ABOoL**

ADA anti-drug antibodies AΕ adverse event

AECA Anti-epithelial cell antibody ALT alanine aminotransferase AST aspartate aminotransferase

 AUC_{0-24} area under the plasma concentration-time curve from pre-dose (time₀) to 24 hours

 $AUC_{0-\infty}$ area under the plasma concentration-time curve from pre-dose (time₀) to infinity

BLQ below the limit of quantification

BMI body mass index BUN blood urea nitrogen

complement component 1q C1q C3 complement component 3

CAR-T chimeric antigen receptor and T-cell

CFR Code of Federal Regulations CIC circulating immune complexes

 C_{max} maximum plasma concentration determined directly from the concentration-time

profile

CRO contract research organization

CVcoefficient of variation

CVID common variable immune deficiency

D5W dextrose 5% in water

DEC Dose Escalation Committee direct immunofluorescence DIF DLT dose-limiting toxicity DNA deoxyribonucleic acid

desmoglein Dsg

ECG electrocardiogram

eCRF electronic case report form **EDC** electronic data capture ET early termination

FCGR2A Fc gamma R2a receptor FcRn neonatal Fc receptor

FDA Food and Drug Administration

GCP Good Clinical Practice

 H_2 histamine₂ **HBV** hepatitis B virus **HCV** hepatitis C virus HIPAA Health Insurance Portability and Accountability Act

HIV human immunodeficiency virus
HR-QoL health-related quality of life
IB Investigator's Brochure
IC immune complex

IC immune complex
ICF Informed Consent Form

ICH International Council on Harmonisation

IgA immunoglobulin A
IgG immunoglobulin G
IgG1-4 immunoglobulin G1-G4
IgM immunoglobulin M
IND investigational new drug
IRB institutional review board

IUD intrauterine IV intravenous

IVIG intravenous immunoglobulin

mAb monoclonal antibody
MED minimum effective dose

MedDRA Medical Dictionary for Regulatory Activities

NCI CTCAE National Cancer Institute Common Terminology Criteria for Adverse Events

NHP nonhuman primate

NOAEL no observed adverse effect level

PD pharmacodynamics

PDAI Pemphigus Disease Area Index

PK pharmacokinetic

QTcF corrected QT interval using Fridericia's formula

RNAseq RNA sequencing
SAE serious adverse event
SAP statistical analysis plan
SAS Statistical Analysis System

SD standard deviation

SNP single nucleotide polymorphism

SOC system organ class

SYNT001 a humanized, affinity matured IgG4-kappa monoclonal antibody

 $t_{1/2}$ Half-life

TEAE treatment-emergent adverse event

T_{max} observed time to reach peak plasma concentration

ULN upper limit of normal
US United States of America
VZV varicella zoster virus

WAIHA warm autoimmune hemolytic anemia

WHO World Health Organization

WHO-DD World Health Organization Drug Dictionary

2. BACKGROUND AND RATIONALE

SYNT001, a humanized, affinity-matured IgG4-kappa monoclonal antibody (mAb), blocks immunoglobulin G (IgG) and circulating IgG immune complex (CIC) interactions with the neonatal crystallizable fragment receptor (FcRn), and inhibits the varied roles played by FcRn in the immune response.

Through specific and high affinity blockade of FcRn, SYNT001 has been shown to increase the catabolism of IgG and CIC in healthy volunteers and is predicted to block the ability of CIC to activate intracellular signaling events associated with binding to FcRn. This predicts that SYNT001 will also accelerate degradation of endogenous circulating IgG autoantibodies and IgG-IC specifically involved in the pathogenesis of autoimmunity. Blocking FcRn interactions with CICs further predicts that SYNT001 will have consequences for innate and adaptive cellular immunity. In the first instance, blocking multimeric CIC interactions with FcRn within antigenpresenting cells should result in inhibition of CIC inflammatory cytokine production and release by these cells. In addition, as FcRn determines the intracellular itinerary of CICs within and among compartments important in cellular immunity, it is further anticipated that SYNT001 will block antigen processing and presentation of antigens contained within CIC that otherwise lead to CD8⁺ and CD4⁺ T cell activation. Thus, SYNT001 is expected to specifically target immune functions associated with IgG and CIC that are involved in certain IgG-mediated autoimmune conditions.

SYNT001 targets key mechanisms contributing to pathology in a variety of IgG-mediated autoimmune disorders, including warm autoimmune hemolytic anemia (WAIHA) pemphigus, pemphigoid, myasthenia gravis, immune thrombocytopenic purpura (ITP), and chronic inflammatory demyelinating polyneuropathy (CIDP).

While current treatments for certain autoimmune disorders, including chronic steroids, immunosuppressants, intravenous immunoglobulin (IVIG), plasmapheresis, and anti-CD20 mAbs, such as rituximab, can be effective, they are associated with significant adverse effects, and delayed or non-durable responses.

Pemphigus is a rare group of blistering autoimmune diseases that affect the skin and mucous membranes. Autoantibodies are thought to play an important pathogenic role in the mucosal and cutaneous manifestations in patients with pemphigus. Administration of SYNT001, which significantly decreases total IgG levels, including a predicted corresponding decrease in the levels of the pathogenic autoantibodies, may lead to a decrease in the mucosal and cutaneous manifestations in patients with pemphigus. Moreover, the ability of SYNT001 to reduce CICs and the associated innate and adaptive immune responses may allow for further sustained disease modification.

2.1 Study Rationale

This study is being conducted to evaluate the safety, dose, pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity of intravenous (IV) SYNT001 as well as its effects on pemphigus disease activity markers.

2.2 Selection of Doses in this Study

The SYNT001 dose levels for study SYNT001-103 were selected following careful review of the safety, tolerability, and PD effect on total IgG levels studied in non-human primates (NHP) and healthy male subjects.

Four repeat-dose toxicology studies in cynomolgus monkeys examined 2 to 14 repeat weekly IV doses 5 to 100 mg/kg SYNT001 with up to a 4-week follow-up. There was one death in the 14-week study attributed to an immune-evoked infusion reaction, which correlated with the development of ADAs, circulating immune complexes, circulating complement depletion, and deposition of immune complexes containing SYTN001 and complement in tissues. Across studies, clinical signs were limited to reports of transient emesis/vomitus following dosing and facial flushing and periocular swelling observed in the 5-week study after the third dose coincident with the first appearance of ADAs. With the exception of emesis/vomitus, these clinical signs were effectively controlled with diphenhydramine pretreatment in the 5-week study and the subsequent 14-week study. There were no adverse SYNT001-related changes in weight gain, clinical chemistry, gross or histo-pathology. The No Observed Adverse Effect Level (NOAEL) was the highest dose tested in all 4 studies and the overall NOAEL following repeat weekly exposure to STYNT001 of up to 14 doses in cynomolgus monkeys was 100 mg/kg.

The safety, tolerability, and PD effect on total IgG levels in study SYNT-101—a Phase 1a study that assessed single ascending doses of SYNT001 in healthy male subjects—were also reviewed. In study SYNT-101, the doses of SYNT001 up to and including 30 mg/kg were well tolerated. There were no dose-limiting toxicities, serious adverse events (SAEs), or any other safety concerns. No adverse events (AEs) were observed in the 1 and 3 mg/kg dose cohorts. Headache was the most commonly reported treatment-emergent adverse event (TEAE), occurring in 8 of 11 subjects treated with 10 or 30 mg/kg SYNT001. One headache in the 10 mg/kg cohort was moderate (Grade 2) in severity; all other headaches were mild (Grade 1). One mild headache was treated with a single dose of acetaminophen; all other headaches resolved without treatment. Therefore, it is anticipated that the doses selected for this study should be well tolerated and have clinically relevant PD effects in patients with pemphigus.

Further consideration was given to the desired level of FcRn blockade to achieve suppression of IgG to a range that has been previously correlated with disease remission induced by immunoadsorption in autoimmune disorders such as pemphigus vulgaris and myasthenia gravis (ie, >50% decrease in total IgG from baseline) (Blaha et al., 2011; Eming and Hertl, 2006; Kohler et al., 2011).

The Sponsor also considered the potential effects of inhibiting FcRn function as they relate to IC associated innate and adaptive immunity. From the NHP studies, single doses of SYNT001 produced a dose-dependent decrease in total IgG and a further decrease was seen with repeated weekly doses up to a maximum 70% reduction at 100 mg/kg. This magnitude of total IgG reduction is approaching the expected maximal effect of 100% inhibition of FcRn function based on murine studies performed by the Sponsor and others (Nixon et al., 2015; Roopenian et al., 2003). In the recently completed Phase 1a trial with SYNT001 in healthy volunteers a single dose caused a maximum average 50% drop in total IgG with IV dosing at 30 mg/kg. Based on the NHP studies further reductions are expected following multiple dosing. A comparable

decrease in pathogenic autoantibodies is anticipated. In study SYNT-101, a single dose caused a maximum average 50% drop in total IgG with IV dosing at 30 mg/kg. Based on the NHP studies, further reductions may occur following multiple dosing.

For more information on the findings from the clinical and nonclinical findings with SYNT001, please refer to the Investigator's Brochure (IB).

2.3 Compliance Statement

This study will be conducted in compliance with Good Clinical Practice (GCP), including the International Conference on Harmonisation (ICH) Guidelines and FDA regulations, consistent with the principles outlined in the Declaration of Helsinki. In addition, the Investigator agrees to adhere to all applicable local laws and regulatory requirements relevant to the use of new therapeutic agents.

The study will be conducted in compliance with the protocol. The appropriate Institutional Review Boards (IRBs) must approve the protocol, any amendments, and the subject informed consent form (ICF) prior to implementation.

Freely given written informed consent must be obtained from every subject prior to participation in this clinical trial. As part of this procedure, the Investigator must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the study subject is aware of the potential risks, inconveniences, or AEs that may occur. The study subject should be informed that he/she is free to withdraw from the study at any time. He/she will receive all information that is required by federal regulations and ICH guidelines. The Investigator or designee will provide the Sponsor with a copy of the IRB-approved informed consent form prior to the start of the study. The rights, safety, and well-being of participating subjects are the most important considerations and should prevail over interests of science and society.

Study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). This trial will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

3. STUDY OBJECTIVES AND ENDPOINTS

3.1 Primary Objective

The primary objectives of this study are as follows:

- Safety: To evaluate the safety of once-weekly IV infusions of SYNT001 at different dose levels and dosing durations in subjects with pemphigus (vulgaris or foliaceus)
- Dose Selection: To determine a Minimum Effective Dose (MED) of SYNT001 as assessed by (i) total IgG level nadir and (ii) the proportion of subjects that meet the criteria for response by Pemphigus Disease Area Index total activity score (PDAI)

3.2 Secondary Objectives

The secondary objectives of this study are as follows:

- To determine the pharmacokinetics (PK) of SYNT001 following once-weekly IV infusions at different dose levels and dosing durations
- To evaluate the effect of once-weekly doses of SYNT001 at different dose levels and dosing durations on PD biomarkers
- To assess the effect of once-weekly doses of SYNT001 at different dose levels and dosing durations on disease markers
- To measure the immunogenicity of once-weekly doses of SYNT001 at different dose levels and dosing durations

3.3 Exploratory Objectives

The exploratory objectives of this study are as follow:

- To explore the effect of once-weekly doses of SYNT001 at different dose levels and dosing durations on biomarkers to understand the pathophysiology of the disease and the SYNT001 mechanisms of action
- To determine the impact of different SYNT001 dose levels and dosing durations on the subject's use of corticosteroids to treat their pemphigus (vulgaris or foliaceus)
- To assess the impact of once-weekly doses of SYNT001 on the subject's health-related quality of life (HR-QoL) at different dose levels and dosing durations
- To assess the effect of once-weekly doses of SYNT001 on the appearance of skin and mucosal lesions at different dose levels and dosing durations
- To quantify the amount of SYNT001 in skin (skin biopsies optional)

3.4 Primary Endpoints

The primary endpoints of this study are as follows:

Safety: The evaluation of SYNT001 safety based on vital signs, physical examinations, electrocardiograms (ECGs), clinical safety laboratory tests, the incidence of adverse events

Dose Selection: The determination of dose and dosing duration of SYNT001 that achieves (i) total IgG level nadir decrease by \geq 60% and \leq 90% from baseline and (ii) a PDAI total activity score of \geq 50% reduction from baseline to allow further clinical development in subject with pemphigus (vulgaris or foliaceus)

3.5 Secondary Endpoints

The secondary endpoints of this study are as follows:

- The determination of PK parameters including half-life (t_{1/2}), maximum serum concentration determined directly from the concentration-time profile (C_{max}), observed time of peak plasma concentration (T_{max}), area under the serum concentration-time curve from pre-dose (time₀) to 24 hours post-dose (AUC₀-2₄), and area under the serum concentration-time curve from pre-dose (time₀) to infinity (AUC₀-∞), (Cohort 1); maximum plasma concentration determined directly from the concentration-time profile (C_{max}) and T_{max} (Cohort 2 onwards) summarized by cohort and timepoint
- The evaluation of PD biomarkers based on absolute serum levels and percent change from baseline in serum levels of total immunoglobulin G (IgG), IgG subtypes (IgG1-4), immunoglobulin A (IgA), immunoglobulin M (IgM), albumin, and CIC summarized by cohort and timepoint
- The assessment of pemphigus disease activity by responses on PDAI based on absolute and percent change from baseline will be summarized by cohort and timepoint
- The assessment of pemphigus disease pathogenic antibody levels based on absolute and percent change from baseline of serum anti-desmoglein 1 and 3 antibody (anti-Dsg 1 and anti-Dsg 3) levels that will be summarized by cohort and timepoint
- The immunogenicity of once-weekly administered SYNT001 as determined by presence of anti-SYNT001 binding antibodies and neutralizing antibodies summarized by cohort and timepoint

3.6 Exploratory Endpoints

The exploratory endpoints of this study are as follows:

- The exploration of SYNT001 mechanisms of action and effects of SYNT001 on pathophysiology summarized by cohort and timepoint as determined by:
 - Complement component 3 (C3) levels by nephelometry
 - Anti-epithelial cell antibody (AECA) titers by indirect immunofluorescence
 - Fc gamma R2A receptor (FCGR2A) single-nucleotide polymorphisms (SNP) by genotyping
 - Presence of disease and inflammatory markers by RNAseq (RNA sequencing)
 - Immunophenotyping via measures of T cells, monocytes, NK cells and B cells by flow cytometry
 - Urine IgG levels to explore SYNT001 distribution and elimination

- Exploratory biomarkers to investigate immune response associated with pemphigus
- The evaluation of corticosteroid use during the study will be summarized by cohort and timepoint
- The assessment of SYNT001 impact on subject's HR-QoL by responses to the Autoimmune Bullous Disease Quality of Life (ABQoL) questionnaire and Skindex-29 scores summarized by cohort and timepoint
- The qualitative assessment of changes in appearance of skin and mucosal lesions as determined by photography presented by cohort and timepoint
- The determination of SYNT001 levels in skin biopsies across timepoints (skin biopsies optional)

Further details on the statistical and analytical plans for these endpoints are available in Section 11.

4. STUDY DRUG

4.1 Description of SYNT001

SYNT001 is provided in vials containing 5 mL SYNT001 (extractable volume) at a nominal concentration of 50 mg/mL. The product is supplied as a liquid at pH 6.5 ± 0.5 . SYNT001 is diluted in dextrose 5% in water (D5W) to prepare the solution for infusion. SYNT001 will be infused via IV in 250 mL over 1 hour \pm 15 minutes using a 0.2-micron, inline filter.

For detailed information regarding SYNT001 preparation and administration, refer to the Pharmacy Manual.

4.2 Dose Requirements

The specification for host cell deoxyribonucleic acid (DNA) in SYNT001 is <2 pg/mg, the limit of quantitation of the assay. To comply with regulatory guidelines, which specify a maximum level of 10 ng host cell DNA per dose, dosing per subject is limited to 5000 mg SYNT001.

For example, a subject with a body weight of 166 kg and enrolled in the ≤30 mg/kg dose cohort will receive ≤4960 mg SYNT001 per dose. If a subject's body weight extrapolates to an expected dose ≥5000 mg SYNT001, the dose will be capped to ensure the 5000 mg SYNT001 per dose limit is not exceeded.

A subject with a body weight of 111 kg and enrolled in the ≤45 mg/kg dose cohort will receive ≤4995 mg SYNT001 per dose. If a subject's body weight extrapolates to an expected dose ≥5000 mg SYNT001, the dose will be capped to ensure the 5000 mg SYNT001 per dose limit is not exceeded.

4.3 Handling and Storage of SYNT001

All supplies of SYNT001 will be provided by the Sponsor and must be stored refrigerated (2°C to 8°C/36°F to 46°F) in the carton and protected from light, in a securely locked area, accessible to authorized persons only, until needed for dose preparation.

4.4 Study Drug Accountability

The Investigator (or designee) is responsible for maintaining accurate accountability records of the study drug throughout the clinical study. Qualified site personnel will inventory the study drug received and will maintain records of disposition of the drug, including dates, quantity and use. All study drug received at the site must be accounted for on an accountability log provided by the Sponsor. All dispensing and accountability records will be available for Sponsor review. Study drug accountability will be verified during on-site monitoring visits.

Upon the completion or termination of the study, and upon written authorization from the Sponsor, or its representative, all unused and/or partially used study drug should be returned or destroyed at the investigational site, as specified by Sponsor. It is the Investigator's responsibility to ensure that the Sponsor, or its representative, has provided written authorization that procedures for proper disposal of the study drug have been established, and that appropriate

records of the disposal are documented and maintained. No unused study drug may be disposed of until fully accounted for by the Sponsor monitor (or designee).

5. STUDY DESIGN

5.1 Study Sites

This study will be conducted at approximately 10 global study sites.

5.2 Overview of Study Design

This is a multicenter, open-label safety study to determine the dose regimen of SYNT001 administered intravenously in subjects with pemphigus (vulgaris or foliaceus). Approximately 20 (up to a maximum of 32) eligible subjects will receive planned doses of 10 mg/kg up to 45 mg/kg of SYNT001.

Cohorts will be dosed sequentially beginning with Cohort 1. Up to 8 eligible subjects will be enrolled in Cohort 1 and will receive 5 once-weekly 60-minute infusions of SYNT001 10 mg/kg. Based on review of safety, PD, and clinical outcomes of Cohort 1, sequential cohorts will enroll, pending recommendation received from a scheduled Dose Escalation Committee (DEC) review.

The DEC will consist of the Medical Monitor, an Independent Clinical Expert and a Syntimmune Medical Officer. To assist in the safety assessments, the DEC may request that Investigators, other experts, or members within their organization review the data and participate in the discussions.

Each cohort must be fully enrolled before a successive cohort will be opened for enrollment. An overview of the study cohorts is provided in Table 5 and Figure 1 shows a schematic of the study design.

Table 5. Cohort Overview

Cohort No.	No. of Subjects	SYNT001 Dose	No. of Doses	DEC Review Timepoint
1 ^a	up to 8	10 mg/kg	5	NA
2 ^b	4 ^c	≤30 mg/kg ^d	5	When 100% of Cohort 1 subjects reach Day 42
3 ^b	4°	≤30 mg/kg ^d	14	When 50% of Cohort 2 subjects reach Day 42
4 ^b (optional)	4 ^c	≤45 mg/kg ^d	≤14	When 50% of Cohort 3 subjects reach Day 42 ^e

Abbreviations: DEC = Dose Escalation Committee; NA = not applicable

- a. No more than 3 subjects with pemphigus foliaceus may be enrolled
- b. Two or fewer subjects with pemphigus foliaceus may be enrolled
- c. Up to 4 additional subjects may be added following DEC's evaluation.
- d. Dose will be recommended by the DEC and will be based on both an ongoing and set timepoint review of safety and pharmacodynamic evaluations including but not limited to, dose-limiting toxicities (DLTs), adverse events (AEs), treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and total IgG levels.
- e. All available data will be considered.

The first 2 subjects in Cohorts 1 and 2 will be enrolled at staggered intervals to facilitate adequate safety evaluation before dosing of subsequent subjects may proceed. A staggered

dosing interval for the first 2 subjects enrolled in successive cohorts will not be required if the planned dose is equal to or lower than that previously administered.

At 24-hour and 7-day intervals described below, the DEC will review of all available safety data (including but not limited to dose limiting toxicities [DLTs], AEs, TEAEs, and SAEs, PD (including but not limited to IgG levels), and clinical outcomes.

DEC Safety Review of 24-hour Data for Cohorts 1 and 2, Subject 1

The first 2 subjects will be dosed at least 24 hours apart. A DEC review of the 24-hour safety data for the first subject will be performed to ensure that there are no overt safety concerns before dosing the second subject.

Safety Review of 7-day Data for Cohorts 1 and 2, Subjects 1 and 2

The 7-day safety data for the first 2 subjects will be performed prior to dosing the remaining subjects in the cohort.

The 24-hour and 7-day reviews will consider seriousness and severity of AEs/TEAEs/SAEs and relatedness to study drug, vital sign assessments, physical examinations, and clinical laboratory testing.

For further information about dose escalation and study stopping rules, refer to Section 9.5.1 and Section 9.5.2, respectively.

5.3 Randomization and Blinding

This is an open-label study.

6. STUDY POPULATION

6.1 Target Population

This study will be conducted in approximately 20 male and female subjects aged 18 and older with a confirmed diagnosis of pemphigus (vulgaris or foliaceus).

Up to 8 subjects may be enrolled in Cohort 1. Four subjects will be enrolled sequentially in Cohort 2, 3, and 4 (optional cohort). An additional 4 subjects may be enrolled in Cohorts 2, 3 and 4 (optional cohort) following DEC's evaluation and recommendation.

Subjects who withdraw for any reason other than an AE and who do not receive study drug or have only received one dose of study drug may be replaced, up to one subject per cohort. Thus, the maximum number of subjects who may be enrolled in this study is 36 (20 + up to 12 additional subjects, + up to 4 replacements, as necessary).

Within Cohort 1, no more than 3 subjects may be enrolled with pemphigus foliaceus. Within successive cohorts, ≤ 2 subjects with pemphigus foliaceus may be enrolled.

Subjects will be enrolled only once in the study and will not be included in subsequent dosing cohorts. Subjects who do not receive all doses of study drug will continue to be followed through all scheduled visits.

6.2 Inclusion Criteria

A subject must meet the following criteria to be eligible for the study:

- 1. Willing and able to read, understand, and sign an informed consent form.
- 2. Male or female ≥ 18 years of age at the time of screening.
- 3. Documented diagnosis of pemphigus vulgaris or foliaceus based on all 3 of the following criteria:
 - a. Documented clinical history consistent with pemphigus vulgaris or foliaceus (clinical presentation defined as mucosal and/or skin lesions).
 - b. Presence of Anti-Dsg 1 or 3 antibodies above the upper limit of normal (ULN).
 - c. History of at least one positive tissue-based test (eg, biopsy, direct immunofluorescence [DIF]).
- 4. Active disease defined as lesions lasting >2 weeks, and 3 active lesions in skin or mucosa or 2 active lesions with at least one being a skin lesion >1 cm diameter:
 - a. If treated with rituximab or other anti-CD20 mAb, last dose >12 months prior to screening.
 - b. If being treated with other immunosuppressants (ie, azathioprine, mycophenolate mofetil, methotrexate, dapsone, cyclosporine, tacrolimus, sirolimus, or low-dose cyclophosphamide [\leq 100 mg/day]), dose must be stable, defined as <25% change in dose, for 4 weeks prior to screening.
 - c. On stable dose of corticosteroids, defined as ≤1 mg/kg of prednisone or equivalent and may not be increased by more than 50% in the 2 weeks prior to screening.

- d. Allowed topical therapies for pemphigus lesions upon entering the study include petroleum jelly or Aquaphor® for the skin or chlorhexidine for the mouth.
- e. Stable use of topical low strength hydrocortisone ($\leq 1\%$), tacrolimus, sirolimus, or pimecrolimus for lesions contributing < 10% of the PDAI total activity score for the 4 weeks prior to screening is allowed. Stable use of dexamethasone elixir solution (swish and spit only) for oral lesions for the 4 weeks prior to screening is allowed.
- f. If not on regular corticosteroids, no pulse corticosteroids are allowed in the 2 weeks prior to screening.
- 5. Body mass index (BMI) $> 18.5 \text{ kg/m}^2$.
- 6. Has a negative pregnancy test documented prior to the first dose of study drug (for women of childbearing potential).
- 7. Females of childbearing potential must agree to be abstinent or else use any two of the following medically acceptable forms of contraception (<1% per year failure rate) from the screening period through the final study visit: oral contraceptive, condom with or without spermicidal jelly, diaphragm or cervical cap with spermicidal jelly, or intrauterine device (IUD). A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception.
- 8. Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months do not require contraception during the study.
- 9. Males with female partners of childbearing potential, including males who are surgically sterile (post vasectomy), must agree to be abstinent or else use a medically acceptable form of contraception from the screening period through 60 days after the final study visit.
- 10. A PDAI total activity score of >4 at screening.

6.3 Exclusion Criteria

A subject who meets any of the following criteria is ineligible for the study:

- 1. Subject unable or unwilling to comply with the protocol.
- 2. Active non-hematologic malignancy or history of non-hematologic malignancy in the 3 years prior to screening (exclusive of non-melanoma skin cancer and cervical cancer in situ).
- 3. Positive for human immunodeficiency virus (HIV) or hepatitis C antibody.
- 4. Positive for hepatitis B surface antigen.
- 5. Active infection or history of recurrent infections.
- 6. IVIG treatment within 30 days of screening.
- 7. Received any cytotoxic (other than azathioprine) or any non-anti-CD20 mAb therapy in the 3 months prior to screening.
- 8. Any exposure to an investigational drug or device within the 30 days prior to screening.
- 9. Plasmapheresis or immunoadsorption within 30 days of screening.
- 10. Cellular therapy, including chimeric antigen receptor and T-cell (CAR-T), at any time prior to screening.
- 11. Use of any systemic or topical immunosuppressive drugs within 3 months of screening not including dose allowed by the inclusion criteria.
- 12. Serum total IgG <600 mg/dL.

- 13. Subject has any current medical condition that, in the opinion of the Investigator, may compromise their safety or compliance, preclude successful conduct of the study, or interfere with interpretation of the results (eg, a significant pre-existing illness or other major comorbidity that the Investigator considers may confound the interpretation of the study results).
- 14. Any vaccination within 2 weeks of screening.

7. STUDY PROCEDURES

7.1 Informed Consent

All subjects must take part in the informed consent process. Adequate time must be allowed for the subject to ask questions and make a voluntary decision. No protocol-specific procedures, including screening procedures are to be performed until the subject has signed and dated an IRB-approved ICF. Subjects may withdraw consent at any time. Participation in the study may be terminated at any time without the subject's consent as determined by the Investigator.

7.2 Demographics and Medical History

Demographics (age, gender, race and ethnicity) and medical history will be obtained from the subject and recorded on the source document and electronic case report form (eCRF). Medical history will capture the subject's current medical history (current disease processes), past medical status (past disease processes), history of surgery, concomitant treatments, and relevant clinical response to past disease specific treatments including duration and dosing of such treatments.

7.3 Physical Examination

A complete physical examination will include measurements of weight (in kg) and height (in cm; height to be measured only at screening visit) and a review of the following body systems:

- General appearance
- Head, eyes, ears, nose, and throat
- Neck
- Respiratory
- Cardiovascular
- Abdomen
- Neurologic
- Extremities
- Dermatologic
- Lymphatic

Any abnormal and clinically significant findings from the physical examination must be recorded in the appropriate eCRF. Findings at screening and Day 0 (pre-dose) will be recorded as medical history.

7.4 Vital Sign Measurements

Vital sign assessments will include measurements of sitting blood pressure (mm Hg), heart rate (beats per minute), respiration rate (breaths per minute), pulse oximetry, and oral temperature (Celsius). Abnormal results are to be repeated after 5 minutes of rest. See Table 6 for timing window allowances with respect to measurement collection.

Vital sign measurements will be collected after the subject has been sitting for 5 minutes. Subjects should be seated quietly for at least 5 minutes in a chair with their backs supported, their feet flat on the floor (legs uncrossed), and their arms bared on a hard surface, with the arm slightly abducted and bent, with palm up and the midpoint of upper arm at heart level. Correct cuff and bladder size should be utilized and the same cuff and arm should be used per subject throughout study.

Vital sign measurements are to be obtained immediately prior to the infusion; 15, 30, and 45 minutes after the start of the infusion; at completion of the infusion; 30 minutes, 1 hour, and 2 hours following completion of the infusion. Abnormalities in vital sign measurements will be graded in severity per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) scale Version 4.03.

Table 6. Timing Windows for PK/PD Sampling, ECG, and Vital Sign Measurements

Time Point	Tolerance Window						
	Cohort 1	Cohorts 2, 3, and 4 (Optional Cohort)					
Pharmacokinetic Sampling							
0 hour	-240 minutes to 0 hour	-240 minutes to 0 hour					
5 minutes post end-of-infusion	±5 minutes	±5 minutes					
1 hour post end-of-infusion	N/A	±15 minutes					
2 hours post end-of-infusion	±15 minutes	±15 minutes					
4 and 6 hours post end-of-infusion	±15 minutes	N/A					
24 hours (1 day) post end-of-infusion	±60 minutes	N/A					
48 hours (2 days) post end-of-infusion	±120 minutes	N/A					
Pharmacodynamic Sampling							
0 hour	-240 minutes to 0 hour	-240 minutes to 0 hour					
24 hours (1 day) post end-of-infusion	±60 minutes	N/A					
48 hours (2 days) post end-of-infusion	±120 minutes	N/A					
ECG							
5 minutes post end-of-infusion	±10 minutes	±10 minutes					
Vital Signs ^a							
0 hour	-240 minutes to 0 hour	-240 minutes to 0 hour					
15, 30, and 45 minutes after start of infusion	±5 minutes	±5 minutes					
1 hour after start of infusion	±10 minutes	±10 minutes					
30 minutes, 1 and 2 hours post end-of-infusion	±10 minutes	±10 minutes					

Abbreviations: ECG = electrocardiogram; N/A = not applicable; PD = pharmacodynamic; PK = pharmacokinetic.

a. Vital signs to include blood pressure, pulse rate, respiratory rate, oral temperature, and pulse oximetry.

7.5 Clinical Laboratory Measurements

Laboratory testing (hematology, urinalysis, serum chemistry, virology, serology, pregnancy tests, PD samples, PK samples, and ADA samples) will be performed using established methods by a central laboratory. Clinical safety laboratory panels are listed in Table 7. Blood and urine samples for hematology, serum chemistry, and urinalysis will be prepared using standard procedures. Results will be provided to the Investigator. Aliquots from the PK, biomarker and ADA samples may be retained as back-up for additional testing as necessary. Subjects will be in a seated or supine position during blood collection. Collection times for all safety, PD, and exploratory labs are outlined in Table 2, Table 3, and Table 4.

Table 7. Clinical Safety Laboratory Panels

Hematology	Serum Chemistry	Urinalysis	Virology
 CBC with differential and blood smear Erythrocyte sedimentation rate 	 Albumin Alkaline phosphatase ALT AST BUN C-Reactive Protein Calcium Carbon dioxide Chloride Creatinine Glucose LDH Phosphorus Potassium Sodium Total and direct bilirubin Total protein Uric acid 	 Appearance Color pH Specific gravity Ketones Protein Glucose Nitrite Urobilinogen Blood/hemoglobin Leukocyte esterase Bilirubin Microscopic examination of sediment: only if the results of the urinalysis dipstick evaluation are positive for blood/hemoglobin 	 Hepatitis C Hepatitis B HIV Tetanus VZV

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; VZV = Varicella-Zoster virus.

Abnormalities in clinical laboratory tests that are considered clinically significant are to be recorded on the AE eCRF page. Laboratory results will be graded using the NCI CTCAE, Version 4.03. If laboratory values constitute part of an event that meets criteria defining it as serious, the event (and associated laboratory values) must be reported as an SAE (see Section 10.2.3).

For Cohort 1, the total blood draw for each subject who completes the study at Day 112 will be approximately 420 mL. For Cohort 2 the total blood draw for each subject who completes the study at Day 112 will be approximately 380 mL. For Cohort 3 and Cohort 4 (Optional), the total

blood draw for each subject who completes the study at Day 175 will be 656 mL. Please refer to the Laboratory Manual for more information.

7.5.1 Pregnancy Testing

Pregnancy testing will be performed for women of childbearing potential. Urine or serum test is acceptable; however, positive urine tests must be confirmed with serum testing.

7.5.2 Virology

Testing for hepatitis C antibody, hepatitis B surface antigen, and HIV antibody will be performed at screening.

7.5.3 Serum Tetanus Antibody and Varicella-Zoster Virus Antibody Testing

Samples for serum tetanus antibody and VZV antibody testing are to be collected at baseline (pre-dose, Day 0), during the follow-up period, and at the end-of-study visit. Any subject whose baseline value for tetanus or VZV was above the detectable level at baseline, and is not within 30% of the baseline value or is below the protective level by the end-of-study visit, will be referred to their primary care physician for further management.

7.5.4 Pharmacokinetics (PK) Sampling

The following PK parameters will be studied in Cohort 1: $t_{1/2}$, C_{max} , T_{max} , AUC_{0-24} , and $AUC_{0-\infty}$. For all successive cohorts, the PK parameters studied will be C_{max} and T_{max} .

Specific collection times are detailed in Table 6. Detailed instructions for sample collection and preparation will be provided in a separate laboratory manual

7.5.5 Pharmacodynamic Sampling

PD samples will be collected for analyses throughout the study. Measurements for albumin will be derived from the clinical safety laboratory results. Specific collection times are detailed in. Samples for each type of PD will be collected according to the schedule shown in Table 8.

Table 8. Pharmacodynamic Assessments

Parameter	Collection Time Points		
	Cohort 1	Cohort 2	Cohort 3
IgGIgG subtypes (IgG1-4)IgAIgM	Screening and Days 0, 1, 2, 5, 7, 12, 14, 19, 21, 28, 29, 30, 33, 42, 56, 84, and 112	Screening and Days 0, 7, 14, 21, 28, 35, 42, 56, 84, and 112	Screening and Days 0, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, 91, 98, 105, 119, 147, and 175
Circulating immune complexes (CIC)	Days 0, 5, 7, 12, 14, 19, 21, 28, 33, 42, 56, 84, and 112	Days 0, 7, 14, 21, 28, 35, 42, 56, 84, and 112	Days 0, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, 91, 98, 105, 119, 147, and 175
Albumin	Screening and Days 0, 7, 14, 21, 28, 33, 42, 56, 84, and 112	Screening and Days 0, 7, 14, 21, 28, 35, 42, 56, 84, and 112	Screening and Days 0, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, 91, 98, 105, 119, 147, and 175
Anti-Dsg (1 and 3) antibody titers	Screening and Days 0, 7, 14, 33, 56, 84, and 112	Screening and Days 0, 7, 14, 21, 28, 35, 42, 56, 84, and 112	Screening and Days 0, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, 91, 98, 105, 119, 147, and 175
C3 and AECA levels by indirect immunofluorescence	Days 0, 14, 33, 56, 84, and 112	Days 0, 35, and 56	Days 0, 98, and 119
Exploratory biomarkers (RNAseq, urine IgG)	Days 0, 14, 33, 56, 84, and 112	Days 0, 35, and 56	Days 0, 98, and 119
Immunophenotyping by flow cytometry for measurement of T cells, monocytes, NK cells, and B cells	Days 0, 28, and 56	Days 0, 35, and 56	Days 0, 98, and 119
Exploratory biomarker (FCGR2A SNP, via buccal swab)	Day 0	Day 0	Day 0
Exploratory pemphigus immune response biomarkers	Days 0, 5, 7, 12, 14, 19, 21, 28, 33, 42, 56, 84, and 112	Days 0, 7, 14, 21, 28, 35, 42, 56, 84, and 112	Days 0, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, 91, 98, 105, 119, 147, and 175

See Table 6 for timing window allowances with respect to measurement collection. More information, including detailed instructions for sample collection (including collection tubes) and preparation will be provided in a separate laboratory manual.

7.5.6 Immunogenicity Testing

SYNT001 is being developed for the acute and chronic therapy of autoimmune disorders. Although SYNT001 is a humanized IgG4 mAb, exposure to SYNT001 in clinical trials could result in the development of ADAs, with potential consequences ranging from neutralization with possible lessening of drug efficacy to safety consequences such as allergic reactions. Testing will first detect binding ADAs. Then, for all confirmed positive samples, an ADA titer will be determined and there will be testing for neutralizing effects.

More information, including detailed instructions for sample collection and preparation will be provided in a separate laboratory manual.

7.6 12-Lead Electrocardiogram (ECG)

On dose administration days, digital 12-lead ECG measurements will be obtained at 5 minutes after the completion of the infusion. All ECGs are to be performed with the subject in a supine position having rested in this position for at least 5 minutes before each reading. ECGs are to be performed in triplicate, each at an interval of 1 to 2 minutes apart. See Table 6 for timing window allowances with respect to performing ECG.

The following ECG parameters will be collected: PR interval, RR interval, QRS interval, and QT interval. The ECG findings will be evaluated by a qualified physician for the presence of abnormalities (qualitative assessment). The physician will assess each ECG as normal, abnormal/not clinically significant, or abnormal/clinically significant.

Normal corrected QT interval using Fridericia's formula (QTcF) is ≤450 msec.

Abnormalities in the ECG that appear following therapy or that result in clinical signs and symptoms are considered clinically significant for the purposes of this study and will be recorded on the AE eCRF.

7.7 Pemphigus Disease Area Index (PDAI)

Pemphigus severity and disease activity will be measured using the PDAI in regions where a validated questionnaire is available. A PDAI total activity score will be determined at screening. To be eligible for study participation, the patient's grade by disease severity must be >4. Assuming subject eligibility, the PDAI will be administered during Treatment Period and Follow-up Period. Disease severity categories by PDAI are mild (0 to 8), moderate (9 to 24), and severe (\geq 25) (Shimizu et al., 2014). The Investigator will determine a PDAI score as follows: 0 to 250 points for disease activity (\leq 120 for skin, \leq 10 for scalp, and \leq 120 for mucosa), and 0 to 13 points for damage (\leq 12 for skin and \leq 1 for scalp) (Rosenbach et al., 2009). See Appendix 2.

7.8 Study Drug Administration

SYNT001 will be given as a 250-mL IV infusion over 1 hour \pm 15 minutes using a 0.2-micron, inline filter.

7.9 Photographs

Photographs will be taken of active lesions and follow-up photographs will be taken of the same areas at timepoints indicated in Table 2, Table 3, and Table 4. Subjects who begin a steroid taper will have additional photographs taken at the clinic visit during which the decision to begin the taper is made. A separate manual describing the procedures for taking photographs will be provided.

7.10 Health-Related Quality of Life Assessments

For Cohorts 2, 3 and 4 (optional cohort), health-related quality of life will be assessed using ABQoL and Skindex-29 in regions where a validated questionnaire is available. The ABQoL questionnaire was developed in Australia as a patient-based measure to quantify disease burden, monitor disease activity and evaluate response to therapeutic intervention in patients with autoimmune bullous disease (Sebaratnam et al., 2013; Sebaratnam et al., 2015) (Appendix 3). Skindex-29 was developed to measure the effects of skin disease on patients' quality of life using a self-administered 30 question dermatology survey (Chren et al., 1996) (Appendix 4).

7.11 Adverse Event Assessments

Information regarding the occurrence of AEs will be collected from the time the subject signs the informed consent form and continuing through the last study visit. Findings at screening and Day 0 (pre-dose) will be recorded as medical history. Any known untoward event that occurs beyond the AE reporting period that the Investigator assesses as related to study drug also should be reported as an AE. Clinical AEs will be graded using the NCI CTCAE, Version 4.03 (Appendix 1).

Note: AEs resulting in a subject's permanent discontinuation from the study, regardless of seriousness or relationship to study drug, MUST be promptly reported to the Sponsor. Additionally, subjects must be followed until return to normal and/or resolution of the AE.

See Section 10 for more information.

7.12 Prior and Concomitant Medications

All treatments a subject receives within 14 days prior to enrollment through the end of the study will be documented on the source document and eCRF. A history of treatments taken for the primary disease, even if not taken within the 14 days prior to enrollment, will be collected.

Permitted Medications

Concomitant medication and treatment for co-existing conditions, including those for pemphigus, are permitted if not listed as prohibited.

- 1. Topical antibiotics to treat active infections that occur during the study.
- 2. Topical or systemic treatments for oral candidiasis.
- 3. Topical lidocaine for transient pain relief as needed.
- 4. Concomitant treatment that is medically indicated for any AEs the subject experiences during the study.
- 5. Medication for potential infusion reactions: The Investigator may recommend prophylactic use of acetaminophen, IV hydration, diphenhydramine, histamine₂ (H₂) blockers (eg, ranitidine, famotidine), etc to manage potential infusion reactions.
- 6. Low-strength corticosteroids (eg, hydrocortisone ≤1%) applied to a single lesion contributing <10% of the PDAI total activity score.
- 7. Topical tacrolimus, sirolimus or pimecrolimus applied to a single lesion contributing <10% of the PDAI total activity score.

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- 8. Dexamethasone elixir solution for oral lesions if dose remains stable throughout trial participation (swish and spit only).
- 9. Stable regimen of the following systemic immunosuppressants: azathioprine, mycophenolate mofetil, methotrexate, dapsone, cyclosporine, tacrolimus, sirolimus, or low dose oral cyclophosphamide (≤100 mg/day).

One month after the final dose of SYNT001, corticosteroids may be tapered at the Investigator's discretion.

Prohibited Medications

Use of the following medications will not be permitted during the study unless specified above as permitted:

- 1. Rituximab or other anti-CD20 antibody
- 2. Monoclonal antibodies other than study drug
- 3. Any topical or systemic immunosuppressive drugs apart from those that are listed as permitted.
- 4. IV corticosteroids prior to infusion (except in subjects who received corticosteroids for treatment of a prior infusion reaction to SYNT001)
- 5. Any dietary herbal supplements
- 6. Any investigational drug or device
- 7. Vaccinations within 2 weeks of screening through 28 days following final dose of study drug

7.13 Skin Biopsy

Optional skin biopsy samples from lesional or non-lesional skin will be collected to analyze SYNT001 levels.

8. STUDY ASSESSMENTS

Study assessments are performed on a weekly basis and will be comprised of the following periods: Screening, Treatment (including Baseline [Day 0]), and Follow-Up (including End-Of Study). For those subjects that complete all periods in Cohorts 1 and 2, study duration is 112 days. For those subjects that complete all periods in Cohort 3, study duration is 175 days.

Further detail on specific study assessments is provided in Section 7.

8.1 All Cohorts: Screening Period and First Treatment (Day 0)

8.1.1 All Cohorts: Screening Period (Day -14 to Day -1)

For all cohorts, informed consent must be obtained before any study-specific samples are taken or study-specific tests or evaluations are conducted. The following assessments at the screening visit are to occur within 14 days before dosing. Study eligibility will be based on satisfying all the study inclusion and exclusion criteria (see Section 6).

At the screening visit, information will be collected and subjects will have clinical evaluations as follows:

- Informed consent
- Medical history and demographic data
- Review inclusion and exclusion criteria
- Complete physical examination, including height and weight
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis)
- Pregnancy test
- Hepatitis and HIV screen
- 12-lead ECG (to be obtained in triplicate after 5 minutes of rest in the supine position)
- PD sample collection
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - Anti-Dsg1 and Dsg3 antibody titers
- Concomitant medication assessment
- AE assessment

8.1.2 All Cohorts: Enrollment and First Treatment (Day 0)

For all cohorts, study Day 0 is defined as the date the subject is administered their first dose of study drug. On Day 0, subjects will be asked to come to the clinic and the following procedures will be performed prior to the first dose of study drug:

- Complete physical exam
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry; to be measured immediately prior to the infusion

- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis)
- Pregnancy test
- Serum tetanus antibody and VZV antibody
- PDAI
- PK baseline sample collection (collected just prior to the start of the study drug infusion)
- Immunogenicity sample collection (collected just prior to the start of study drug infusion)
- PD sample collection (collected just prior to the start of the study drug infusion)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titers
 - C3
 - AECA
 - FCGR2A SNP via buccal swab
 - RNAseq
 - Urine IgG
 - Immunophenotyping
 - Exploratory pemphigus immune response biomarkers
- Skin biopsy (optional) (Cohort 1 only)
- Photography
- HR-QoL assessments (ABQoL, Skindex-29) (Cohorts 2 and 3 only)

After the preceding procedures and assessments are completed:

- Study drug administration (record date and time of dose of study drug)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry will be performed at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion

After administration of study drug, the following post treatment procedures and assessments will be performed:

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry: 30 minutes, 1 hour, and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest
- PK sample collection at 5 minutes. Thereafter at 2, 4, 6 hours (Cohort 1) or 1 and 2 hours (Cohorts 2 and 3) after the completion of study drug infusion; record collection date and time for each PK sample
- 12-lead ECG (to be obtained in triplicate at 5 minutes after the completion of study drug infusion

Throughout the study visit, the following assessments will be performed:

- Concomitant medication assessment
- AE assessment

8.2 Cohort 1: Day 1 to 84

8.2.1 Cohort 1: Follow-up Day 1

On Day 1 (24 hours \pm 1 hour from end-of-infusion time on Day 0), the subject will return to the clinic and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature): abnormal results to be repeated after 5 minutes of rest
- PK sample collection (record collection date and time)
- PD sample collection
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
- Skin biopsy (optional)
- Concomitant medication assessment
- AE assessment

8.2.2 Cohort 1: Follow-up Day 2

On Day 2 (48 hours \pm 2 hours from end-of-infusion time on Day 0), the subject will return to the clinic and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature): abnormal results to be repeated after 5 minutes of rest
- PK sample collection (record collection date and time)
- PD sample collection
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
- Skin biopsy (optional)
- Concomitant medication assessment
- AE assessment

8.2.3 Cohort 1: Follow-up Day 5

On Day 5 (120 hours \pm 4 hours from end-of-infusion time on Day 0), subjects may return to the clinic or be visited by an at-home nurse, and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature): abnormal results to be repeated after 5 minutes of rest
- PK sample collection (record collection date and time
- PD sample collection
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Exploratory pemphigus immune response biomarkers
- Concomitant medication assessment
- AE assessment

8.2.4 Cohort 1: Treatment Day 7 (Dose 2)

On Day 7 (\pm 6 hours) subjects will return to the clinic and the following procedures are to be performed prior to study drug infusion:

- Complete physical exam
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry; to be measured immediately prior to the infusion
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis)
- PDAI
- PD sample collection (collected just prior to the start of the study drug infusion)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titers
 - Exploratory pemphigus immune response biomarkers

After the preceding procedures and assessments are completed:

- Study drug administration (record date and time of dose of study drug)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry will be performed at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion

After administration of study drug, the following post treatment procedures and assessments will be performed:

• Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry: 30 minutes, 1 hour, and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest

Throughout the study visit, the following assessments will be performed:

- Concomitant medication assessment
- AE assessment

8.2.5 Cohort 1: Follow-up Day 12

On Day 12 (\pm 6 hours), subjects may return to the clinic or be visited by an at-home nurse, and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature): abnormal results to be repeated after 5 minutes of rest
- PD sample collection
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Exploratory pemphigus immune response biomarkers

- If visit performed at the study site: 12-lead ECG to be obtained in triplicate
- Concomitant medication assessment
- AE assessment

8.2.6 Cohort 1: Treatment Day 14 (Dose 3)

On Day 14 (\pm 6 hours) subjects will return to the clinic and the following procedures are to be performed prior to study drug infusion:

- Complete physical exam
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry; to be measured immediately prior to the infusion
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis)
- PDAI
- Immunogenicity sample collection (collected just prior to the start of study drug infusion)
- PD sample collection (collected just prior to the start of the study drug infusion)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titers
 - C3
 - AECA
 - RNAseq
 - Urine IgG
 - Exploratory pemphigus immune response biomarkers
- Skin biopsy (optional)

After the preceding procedures and assessments are completed:

- Study drug administration (record date and time of dose of study drug)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry will be performed at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion

After administration of study drug, the following post treatment procedures and assessments will be performed:

• Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry: 30 minutes, 1 hour, and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest

Throughout the study visit, the following assessments will be performed:

- Concomitant medication assessment
- AE assessment

8.2.7 Cohort 1: Follow-up Day 19

On Day 19 (\pm 6 hours), subjects may return to the clinic or be visited by an at-home nurse, and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature): abnormal results to be repeated after 5 minutes of rest
- PD sample collection
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Exploratory pemphigus immune response biomarkers
- Concomitant medication assessment
- AE assessment.

8.2.8 Cohort 1: Treatment Day 21 (Dose 4)

On Day 21 (\pm 6 hours) subjects will return to the clinic and the following procedures are to be performed prior to study drug infusion:

- Complete physical exam
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry; to be measured immediately prior to the infusion
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis)
- PDAI
- Immunogenicity sample collection (collected just prior to the start of study drug infusion)
- PD sample collection (collected just prior to the start of the study drug infusion)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Exploratory pemphigus immune response biomarkers

After the preceding procedures and assessments are completed:

- Study drug administration (record date and time of dose of study drug)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry will be performed at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion

After administration of study drug, the following post treatment procedures and assessments will be performed:

• Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry: 30 minutes, 1 hour, and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest

Throughout the study visit, the following assessments will be performed:

- Concomitant medication assessment
- AE assessment

8.2.9 Cohort 1: Treatment Day 28 (Dose 5)

On Day 28 (\pm 6 hours) subjects will return to the clinic and the following procedures are to be performed prior to study drug infusion:

- Complete physical exam
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry; to be measured immediately prior to the infusion
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis)
- PDAI
- PK sample collection (collected just prior to the start of the study drug infusion)
- Immunogenicity sample collection (collected just prior to the start of study drug infusion)
- PD sample collection (collected just prior to the start of the study drug infusion)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Immunophenotyping
 - Exploratory pemphigus immune response biomarkers

After the preceding procedures and assessments are completed:

- Study drug administration (record date and time of dose of study drug)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry will be performed at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion

After administration of study drug, the following post treatment procedures and assessments will be performed:

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry: 30 minutes, 1 hour, and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest
- PK sample collection at 5 minutes and 2, 4, and 6 hours after the completion of study drug infusion; record collection date and time for each PK sample
- 12-lead ECG (to be obtained in triplicate at 5 minutes after the completion of study drug infusion

Throughout the study visit, the following assessments will be performed:

- Concomitant medication assessment
- AE assessment

8.2.10 Cohort 1: Follow-up Day 29

On Day 29 (24 hours \pm 1 hour from end-of-infusion time on Day 28), the subject will return to the clinic and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature): abnormal results to be repeated after 5 minutes of rest
- PK sample collection (record collection date and time)
- PD sample collection
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
- Concomitant medication assessment
- AE assessment

8.2.11 Cohort 1: Follow-up Day **30**

On Day 30 (48 hours \pm 2 hours from end-of-infusion time on Day 28), the subject will return to the clinic and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature): abnormal results to be repeated after 5 minutes of rest
- PK sample collection (record collection date and time)
- PD sample collection
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
- Concomitant medication assessment
- AE assessment

8.2.12 Cohort 1: Follow-up Day 33

On Day 33 (120 hours \pm 4 hours from end-of-infusion time on Day 28), subjects will return to the clinic and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature): abnormal results to be repeated after 5 minutes of rest
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis)
- PDAI
- PK sample collection (record collection date and time)
- PD sample collection
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titers
 - C3
 - AECA
 - RNAseq
 - Urine IgG
 - Exploratory pemphigus immune response biomarkers

- Skin biopsy (optional)
- Photography
- Concomitant medication assessment
- AE assessment

8.2.13 Cohort 1: Follow-up Day 42

On Day 42 (\pm 3 days), subjects will return to the clinic and the following procedures are to be performed:

- Complete physical exam
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature): abnormal results to be repeated after 5 minutes of rest
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis)
- PDAI
- PD sample collection (collected just prior to the start of the study drug infusion)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Exploratory pemphigus immune response biomarkers
- Concomitant medication assessment
- AE assessment

8.2.14 Cohort 1: Follow-up Day 56

On Day 56 (\pm 5 days), subjects are to return to the clinic and the following procedures are to be performed:

- Complete physical exam
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature): abnormal results to be repeated after 5 minutes of rest
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis)
- Pregnancy test
- 12-lead ECG (to be obtained in triplicate after 5 minutes of rest in the supine position)
- Serum tetanus antibody and VZV antibody
- PDAI
- Immunogenicity sample collection
- PD sample collection
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titers
 - C3
 - AECA
 - RNAseq
 - Urine IgG
 - Immunophenotyping

- Exploratory pemphigus immune response biomarkers
- Skin biopsy (optional)
- Photography
- Concomitant medication assessment
- AE assessment.

8.2.15 Cohort 1: Follow-up Day 84

On Day 84 (\pm 5 days), subjects are to return to the clinic and the following procedures are to be performed:

- Complete physical exam
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature): abnormal results to be repeated after 5 minutes of rest
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis)
- Serum tetanus antibody and VZV antibody
- PDAI
- Immunogenicity sample collection
- PD sample collection
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titers
 - C3
 - AECA
 - RNAseq
 - Urine IgG
 - Exploratory pemphigus immune response biomarkers
- Skin biopsy (optional)
- Photography
- Concomitant medication assessment
- AE assessment

Note: Cohort 1 End-of-Study visit is detailed in Section 8.4.

8.3 Cohorts 2 and 3: Subsequent Treatments to Follow-up

8.3.1 Cohort 2: Treatment Days 7 and 21; Cohort 3: Treatment Days 7, 14, 21, 28, 35, 49, 56, 63, 70, 77, and 84

For Cohort 2 Days 7 and 21 (\pm 1 day) and Cohort 3 Days 7, 14, 21, 28, 35, 49, 56, 63, 70, 77, and 84 (\pm 1 day), subjects will return to the clinic and the following procedures are to be performed prior to study drug infusion:

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- Complete physical exam
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry; to be measured immediately prior to the infusion
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis)
- PDAI
- PD sample collection (collected just prior to the start of the study drug infusion)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titers
 - Exploratory pemphigus immune response biomarkers

After the preceding procedures and assessments are completed:

- Study drug administration (record date and time of dose of study drug)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry will be performed at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion

After administration of study drug, the following post treatment procedures and assessments will be performed:

• Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry: 30 minutes, 1 hour, and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest

Throughout the study visit, the following assessments will be performed:

- Concomitant medication assessment
- AE assessment

8.3.2 Cohort 2: Treatment Days 14 and 28; Cohort 3: Treatment Days 42 and 91

For Cohort 2 Days 14 and 28 (\pm 1 day) and Cohort 3 Days 42 and 91 (\pm 1 day), subjects will return to the clinic and the following procedures are to be performed prior to study drug infusion:

- Complete physical exam
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry; to be measured immediately prior to the infusion
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis)
- Pregnancy test (Cohort 3, Days 42 and 91 only)
- PDAI
- PK sample collection (collected just prior to the start of the study drug infusion) (Cohort 2, Day 28 only; Cohort 3, Day 91 only)
- Immunogenicity sample collection (collected just prior to the start of study drug infusion)
- PD sample collection (collected just prior to the start of the study drug infusion)

- IgG, IgG subtypes (IgG1-4), IgA, IgM
- CIC
- Anti-Dsg (1 and 3) antibody titers
- Exploratory pemphigus immune response biomarkers
- Photography (Cohort 3, Day 42 only)

After the preceding procedures and assessments are completed:

- Study drug administration (record date and time of dose of study drug)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry will be performed at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion

After administration of study drug, the following post treatment procedures and assessments will be performed:

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry: 30 minutes, 1 hour, and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest
- PK sample collection at 5 minutes and 1 and 2 hours after the completion of study drug infusion; record collection date and time for each PK sample (Cohort 2, Day 28 only; Cohort 3, Day 91 only)
- 12-lead ECG (to be obtained in triplicate at 5 minutes after the completion of study drug infusion

Throughout the study visit, the following assessments will be performed:

- Concomitant medication assessment
- AE assessment

8.3.3 Cohort 2: Follow-up Days 35 and 56; Cohort 3: Follow-up Days 98 and 119

For Cohort 2 Days 35 (\pm 1 day) and 56 (\pm 3 days) and Cohort 3 Days 98 (\pm 1 day) and 119 (\pm 3 days), subjects are to return to the clinic and the following procedures are to be performed:

- Complete physical exam
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature): abnormal results to be repeated after 5 minutes of rest
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis)
- Pregnancy test (Cohort 2, Day 56 only; Cohort 3, Day 119 only)
- 12-lead ECG (to be obtained in triplicate after 5 minutes of rest in the supine position) (Cohort 2, Day 56 only; Cohort 3, Day 119 only)
- Serum tetanus antibody and VZV antibody (Cohort 2, Day 56 only; Cohort 3, Day 119 only)
- PDAI
- Immunogenicity sample collection (Cohort 2, Day 56 only; Cohort 3, Day 119 only)
- PD sample collection

- IgG, IgG subtypes (IgG1-4), IgA, IgM
- CIC
- Anti-Dsg (1 and 3) antibody titers
- C3
- AECA
- RNAseq
- Urine IgG
- Immunophenotyping
- Exploratory pemphigus immune response biomarkers
- Photography
- HR-Qol (ABQoL, Skindex-29)
- Concomitant medication assessment
- AE assessment

8.3.4 Cohort 2: Follow-up Days 42 and 84; Cohort 3: Follow-up Days 105 and 147

For Cohort 2 Days 42 (\pm 1 day) and 84 (\pm 5 days) and Cohort 3 Days 105 (\pm 1 day) and 147 (\pm 5 days), subjects are to return to the clinic and the following procedures are to be performed:

- Complete physical exam
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature): abnormal results to be repeated after 5 minutes of rest
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis)
- PDAI
- PD sample collection
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - _ CIC
 - Anti-Dsg (1 and 3) antibody titers
 - Exploratory pemphigus immune response biomarkers
- Concomitant medication assessment
- AE assessment

8.4 All Cohorts: End of Study or Early Termination Visit; Cohorts 1 and 2, Day 112; Cohort 3, Day 175

For Cohorts 1 and 2 Day 112 (\pm 5 days) and Cohort 3 Day 175 (\pm 5 days), subjects are to return to the clinic and the following procedures are to be performed:

- Complete physical exam
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature): abnormal results to be repeated after 5 minutes of rest
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis)
- Pregnancy test
- Serum tetanus antibody and VZV antibody

- PDAI
- Immunogenicity sample collection
- PD sample collection
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titers
 - C3 (Cohort 1 only)
 - AECA (Cohort 1 only)
 - RNAseq (Cohort 1 only)
 - Urine IgG (Cohort 1 only)
 - Exploratory pemphigus immune response biomarkers
- Photography
- HR-Qol (ABQoL, Skindex-29) (Cohorts 2 and 3 only)
- Concomitant medication assessment
- AE assessment

Note: a subject may choose to terminate participation in the study at any time. Under this circumstance, the subject will be encouraged to return as soon as possible for an early treatment visit and to receive assessments otherwise scheduled on Day 112 (Cohorts 1 and 2) or Day 175 (Cohort 3).

9. STUDY RULES

9.1 Subject Withdrawal

Every reasonable effort will be made to keep the subject in the study; however, if a subject withdraws from the study, the Investigator should complete and report the reasons for withdrawal as thoroughly as possible. The reason(s) for termination must be clearly documented on the appropriate page of the eCRF.

If a subject discontinues from the study for any reason, every effort will be made to collect all clinical and laboratory data as scheduled for the Early Termination Visit (see Section 8.4). If the subject fails to return for these assessments for unknown reasons, every effort (eg, telephone, email, and letter) should be made to contact them.

The reason(s) for a subject's participation in the study may be prematurely discontinued will be documented and include:

- 1. The subject wishes to withdraw from the study.
- 2. Request by a regulatory agency (eg, Institutional Review Board).
- 3. The subject experiences a significant or intolerable AE.
- 4. The subject experiences a significant adverse change in vital signs, physical examination findings, or clinical laboratory parameter.
- 5. The subject has a need for a concomitant medication that is not permitted by the study protocol.
- 6. The subject experiences generalized impairment or mental incompetence that would result in the subject being unable to understand his or her participation in the study.
- 7. If, in the Investigator's medical judgment, further participation would be injurious to the health and well-being of the subject, or is not in the best interest of the subject.
- 8. Administrative reasons, such as subject non-compliance or a major protocol violation.
- 9. The subject requires a significant increase in dose(s) of anti-pemphigus medication(s) for the management of pemphigus (at the discretion of the Investigator with consultation with the Medical Monitor).

If at the discretion of the Investigator with consultation with the Medical Monitor, a subject requires a significant increase in dose(s) of anti-pemphigus medication(s) for the management of pemphigus, the subject will be encouraged to continue their study visits to allow collection of safety data.

9.2 Subject Replacement

Enrolled subjects withdrawn for a reason other than an AE will be replaced if they have not been dosed or have only received one dose of study drug at the time of discontinuation, up to one subject per cohort. Subjects who do not receive all doses of study drug will continue to be followed through all scheduled study visits.

9.3 Study Discontinuation

The Sponsor has the right to terminate or to stop the study at any time. Reasons for study discontinuation may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other related studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory
- Drug supply issues
- Excessive subject self-withdrawal
- Significant protocol violations (eg, violation of eligibility criteria, dosing errors, missing data for study endpoint analysis)

9.4 Lost to Follow-up

All reasonable effort should be made to contact any subject lost to follow-up during the study to complete assessments and retrieve any outstanding data. If the subject is unreachable after three good faith attempts, at a minimum, the Investigator should follow up with a registered letter requesting contact so safety data may be collected, recorded, and reported (if necessary).

9.5 Stopping Rules

9.5.1 Dose-Escalation Stopping Rule

Dose recommendations will be made by a DEC based upon a review of all available safety data, on a continuous basis as well as at discrete timepoints. Available data will be based on safety and pharmacodynamic evaluations including but not limited to, DLTs, AEs, TEAEs, SAEs, PD (including but not limited to IgG levels), and clinical outcomes.

Dose-limiting toxicity (DLT) will be defined generally as severe (Grade 3) AEs occurring in ≥2 subjects in any cohort that are determined to be clinically significant and considered related to study drug.

If 2 or more subjects at any time in any cohort have Grade 3 AEs that are determined to be clinically significant and considered to be related to study drug, dosing will be halted within that cohort and dose-escalation to a higher dose will not occur. Upon review of the available information, the DEC may reduce the dose prior to enrolling additional subjects using the guidelines below:

- Cohort 1: Dose may be reduced by at least 50%.
- Cohort 2: Dose may be reduced by at least 33%.
- Cohort 3: Dose may be reduced to a level lower than the Cohort 2 dose.
- Cohort 4 (optional cohort): Dose may be reduced to level lower than the Cohort 3 dose.

9.5.2 Study Stopping Rule

If any subject experiences a life-threatening AE (Grade 4) that is considered to be related to study drug, any further dosing in all enrolled subjects will be suspended until the DEC has evaluated the event and determined the next appropriate course of action. At any time during the study, the study may be discontinued if the DEC determines that further drug exposure would pose an undue risk to subjects.

9.5.3 Individual Stopping Rule

Dosing for any individual subject will be discontinued (ie, no further study drug will be given to that subject) if the subject experiences any study drug-related SAE or any study drug-related non-serious AE that, in the judgement of the Investigator (following consultation with the Medical Monitor, if desired) suggest that it could be unsafe to administer further study drug to that subject.

Subjects who are withdrawn from this study due to an AE determined to be related to study drug are to be followed until there is:

- Resolution or stabilization of the AE determined to be related
- The subject is lost to follow-up
- The event is otherwise explained

If there is a persistent AE contributing to discontinuation that is determined to be related to SYNT001, subjects must be followed with appropriate medical management until resolution or stabilization. Refer to Section 10 for more information.

10. EVALUATION OF SAFETY

10.1 Safety Parameters

Subjects will be monitored continuously throughout the treatment and follow-up period for AEs (acute, delayed, and/or cumulative), as well as for changes in clinical status. Parameters measure/assess safety include physical examinations, vital sign measurements (including pulse oximetry), clinical (safety) laboratory tests (hematology, serum chemistries, urinalysis), concomitant medication assessments, and ECG. Clinical and laboratory AEs will be graded using the NCI CTCAE; Version 4.03 (see Appendix 1).

10.2 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical trial subject associated with the use of a drug, whether considered drug related or not. An AE can be an unfavorable and unintended sign (eg, an abnormal laboratory value finding), a symptom, or a disease temporally associated with the use of a drug, without judgment as to causality. An AE can arise from use of the drug (eg, use in combination with another drug) and from any route of administration, formulation or dose, including an overdose. An AE also includes, but is not limited to, any clinically significant worsening of a pre-existing condition. Examples include:

- Any sign, symptom, physical finding, or laboratory result that has worsened in nature, severity or frequency compared to baseline
- Reactions from an investigational drug, including those occurring because of an overdose, abuse of the study drug, withdrawal phenomena, sensitivity or toxicity
- Concurrent illness that was not present or worsens in nature, severity, or frequency compared to baseline
- Injury or accident
- Exacerbation of a pre-existing condition

Pregnancy is not considered an AE or SAE; however, any pregnancy complication(s) should be recorded as an AE(s) or SAE(s) (if applicable). Elective abortions without complications should not be regarded as AEs, unless they were therapeutic abortions. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE. If a female subject becomes pregnant during the conduct of the study, the Investigator must notify the Sponsor according to the procedures provided in Section 10.5.4.

Planned hospitalization admissions or surgical procedures for a condition known to exist before the subject signed the informed consent are not an AE and should be recorded as medical history. If the planned hospitalization or procedure is executed as planned and without complication, the record in the subject's medical history is considered complete. However, if the event/condition deteriorates in an unexpected manner during the study or following surgery, it must be reported as an AE according to the procedures provided in Section 10.2.1.

10.2.1 **Recording an Adverse Event**

For data collection, all untoward events that occur after informed consent through the last study visit are to be recorded on eCRFs by the investigational site. All AEs are to be accurately recorded on the Adverse Event page of the subject's eCRF. The severity of each AE will be graded using the NCI CTCAE, Version 4.03 (see Appendix 1). The date of onset as well as the end date of the event should be recorded or the event should be entered as "ongoing". In addition, the method used to treat the AE and the outcome of the AE will be noted. The Investigator will assess the relationship of the event to study drug.

10.2.2 **Assessment of Causality**

A medically qualified Investigator must assess the relationship of any AE (including SAEs) to the use of the study drug, as related or not related, based on clinical judgment and using all available information. The causal relationship between the study medication and the AE will be assessed using one of the following categories:

Not Related: Factors consistent with an assessment of Not Related include:

- Temporal relationship is lacking (eg, the event did not occur within a reasonable time frame following administration of the study medication); or
- Other causative factors more likely explain the event (eg, a pre-existing condition, other concomitant treatments).

Related: Factors consistent with an assessment of Related include:

- There is a positive temporal relationship (eg, the event occurred within a reasonable time frame following administration of study medication); or
- The AE is more likely explained by the investigational product than by another cause (ie, the AE shows a pattern consistent with previous knowledge of the investigational product or the class of the investigational product)

10.2.3 **Serious Adverse Events**

(Notify Medpace Safety within 24 hours; document on eCRF)

The SAE definition and reporting requirements are in accordance with Title 21 Part Code of Federal Regulations (CFR) 312.32 and the Guidance for Industry and Investigators Safety Reporting Requirements for Investigational New Drug (INDs) and Bioavailability /Bioequivalence Studies.

An AE is considered "serious" if, in the view of either the Investigator or sponsor, it results in any of the following outcomes:

Death: This includes any death that occurs while the subject is "on study" through the last study visit.

Confidential Page 70 of 96 Syntimmune, Inc. **Note:** Death is an outcome of an AE and not an AE. The event(s) that caused death (eg, illness, accident) is the SAE. Death due to any other cause(s) must also be reported as an outcome of the reportable SAE.

- Life-threatening adverse drug event: An AE or suspected adverse reaction is considered "life threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- **Inpatient hospitalization or prolongation of existing hospitalization:** an AE that requires admission to a hospital for medical and/or surgical intervention.
 - In the absence of an AE, the Investigator should not report hospitalization or prolongation of hospitalization as an SAE, as detailed in the following examples:
 - An elective or previously scheduled surgery for a pre-existing condition that has not deteriorated unexpectedly after initiation of treatment (eg, a previously scheduled ventral hernia repair)
 - o Hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol
 - o Hospitalization or prolongation of hospitalization is part of routine procedure followed by study center
 - o Hospitalization for survey visits, annual physicals, or planned observation
 - o Hospitalization for observation with release within 24 hours (eg, an emergency room visit for hematuria that results in a diagnosis of cystitis and discharge to home on oral antibiotics
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect
- Important medical event: An event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.2.3.1 **Recording a Serious Adverse Event**

When the diagnosis of an SAE is known or suspected, the Investigator should record the diagnosis or syndrome as the primary SAE term, rather than as signs or symptoms. Signs and symptoms may then be described in the event description. For example, dyspnea should not be used as an SAE term if the diagnosis, which caused the dyspnea, is known to be malignant pleural effusion.

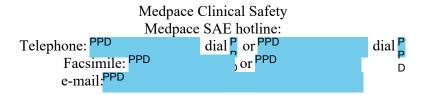
Death should not be recorded as an SAE, but as an outcome of a specific SAE, unless the event preceding the death is unknown. In the exceptional case where the events leading to death are unknown, then death may be used as an event term. If an autopsy was performed, the autopsy the autopsy report should be provided.

10.2.3.2 Reporting a Serious Adverse Event

RESPONSIBILITIES OF THE INVESTIGATOR

Any death, SAE, or pregnancy, experienced by the subject after informed consent through the last study visit, regardless of relationship to study drug, must be promptly reported (within 24 hours of the Investigator becoming aware of the event) by telephone or electronic transmission to the Sponsor (or designee).

Contact information for SAE reporting:



Additionally, the Investigator will be able to contact the **Medical Monitor**:

Medical Safety Contact



The Investigator will report the SAE to his or her IRB in accordance with IRB's standard operating procedures and policies. Adequate documentation must be maintained showing that the IRB was properly notified.

SAEs must be recorded on the SAE form in the electronic data capture (EDC) system. This requirement includes all SAEs that occur after informed consent through the last study visit. The minimum information required for SAE reporting includes identity of investigator, site number, subject number, an event description, SAE term(s), onset date, the reason why the event is serious (ie, the seriousness criteria), and the Investigator's assessment of the relationship of the event to study treatment. Additional SAE information including medications or other therapeutic measures used to treat the event, action taken with the study treatment due to the event, and the outcome/resolution of the event will be recorded. Paper forms for reporting SAEs will be provided to the study sites as back-up in case the EDC system is not accessible.

In all cases, the Investigator should continue to monitor the clinical situation and report all material facts relating to the progression or outcome of the SAE. Furthermore, the Investigator may be required to provide supplementary information as requested by the Sponsor (or designee).

RESPONSIBILITIES OF THE SPONSOR (OR DESIGNEE)

The Sponsor (or designee) will process and evaluate all SAE as soon as the reports are received. For each SAE received, the Sponsor will decide as to whether the criteria for expedited reporting have been met.

The Sponsor (or designee) is responsible for promptly informing the FDA and other regulatory authorities as well as other participating Investigators of the event. Written submission must be made by the Sponsor to the FDA as soon as possible and in no event later than 15 calendar days after the Sponsor's initial notification of the event, or for an event that is fatal or life-threatening no later than 7 calendar days after the Sponsor's initial notification.

EXPEDITED REPORTING

Under FDA ruling (US Code of Federal Regulations, Title 21 CFR Part 312.32) and the ICH Guideline "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A," the Sponsor is required to submit written documentation, in the form of a safety report, detailing:

- Any event associated with the use of the drug, that is both serious and unexpected, or
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.

The Sponsor will submit SAEs that meet the criteria for expedited reporting to the regulatory authorities in accordance with local regulations governing safety reporting.

10.2.4 Follow-Up of Adverse Events and Serious Adverse Events

Any SAE or AE must be followed until either resolution of the event or determination by the Investigator that the event has become stable or irreversible. Appropriate diagnostic tests should be performed and therapeutic measures, if indicated, should be instituted until the event has returned to baseline or until a clinically satisfactory resolution has been achieved. The appropriate follow-up visits must be scheduled and the specific tests repeated or performed as necessary. The status of all AEs will be documented as of the last study visit. If all required information is not available at the time of the initial report, follow-up information will be completed in the EDC system.

10.3 Warnings and Precautions

10.3.1 Vaccinations

Subjects must not receive any vaccinations from within 2 weeks of screening until 28 days following final dose at the discretion of the Investigator.

10.3.2 Management of Allergic or Infusion-Related Reactions

As observed with all mAbs administered by IV infusion, infusion reactions to SYNT001 are possible. In general, infusion reactions to mAbs observed in human studies typically develop

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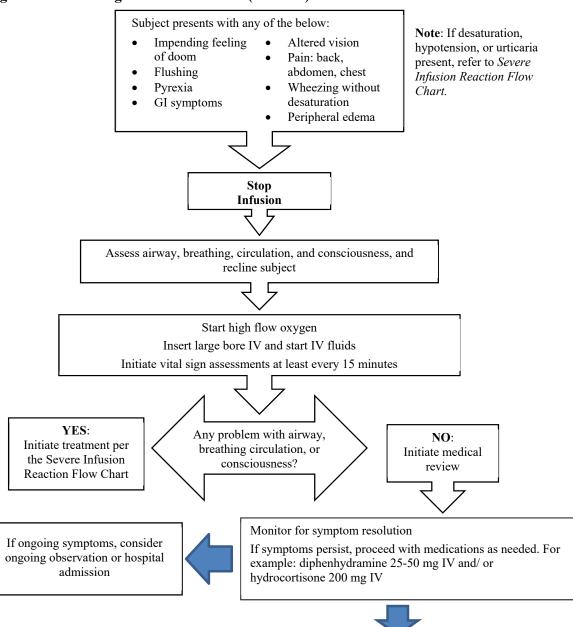
within 30 minutes to 2 hours after the initiation of drug infusion, although symptoms may be delayed for up to 24 hours. These infusion reactions can occur with the first dose of a mAb and are generally mild in severity, although severe and even fatal reactions can occur.

Allergic and/or infusion-related reactions include hypersensitivity reactions and cytokine release syndromes. These reactions are experienced by subjects during or within hours of the infusion of mAb therapy. Symptoms can include flushing, alterations in heart rate and blood pressure, dyspnea, bronchospasm, back pain, fever, urticaria, edema, nausea, and all types of rashes. Anaphylaxis is recognized as a severe, life-threatening, generalized, or systemic reaction. This is a medical emergency characterized by rapidly developing life-threatening airway and/or breathing and/or circulation problems usually associated with skin or mucosal changes.

Management of Grade 1 infusion reactions include interrupting the infusion or decreasing the rate of infusion by 50% and observing. Symptoms may also be treated as needed with medications such as diphenhydramine, hydrocortisone, or acetaminophen, either alone or in combination, depending on the subject's signs and symptoms. If the infusion is interrupted or the infusion rate is decreased, it is important to note that all study drug infusions must be completed within 4 hours of SYNT001 preparation.

Management of Grade 2 and higher infusion reactions should include stopping the infusion of study drug. Continued treatment with SYNT001 is prohibited following Grade 2 or higher infusion reactions. See Figure 2 and Figure 3 for details on the management of Grade 2 and Grade 3 infusion reactions. Allergic or infusion-related reactions will be graded in severity and managed based on NCI CTCAE Version 4.03 (see Table 9).

Figure 2. Management of Moderate (Grade 2) Infusion Reactions



If symptoms and signs resolve completely either spontaneously or after administration of diphenhydramine with or without hydrocortisone, consider rechallenge:

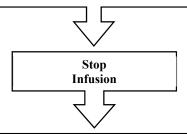
Wait at least 20 minutes following medication administration before commencing rechallenge at an infusion rate of 50% or less of the initial infusion rate or

Consider pre-medicating the subject with the same medication(s) 20-30 minutes in advance of subsequent administrations of SYNT001 and starting infusion at 50% of the planned infusion rate for the first 30 minutes, then returning to the intended infusion rate in the absence of any infusion reaction. If the infusion is interrupted or the infusion rate is decreased, it is important to note that all study drug infusions must be completed within 4 hours of SYNT001 administration.

Figure 3. Management of Severe (Grade 3 or Higher) Infusion Reactions

Subject presents with any of the below:

- Urticaria
- Airway threatened by angioedema
- Angioedema: Lip, mouth, facial swelling
- Respiratory compromise wheezing, dyspnea, stridor or hypoxia (O₂ saturation <90%)
- BP <90 mmHg SBP or >30% decrease from patient baseline



Start basic life support:

- High oxygen flow
- On bed, head down, legs up
- Large bore IV cannula, 1 L normal saline STAT
- Initiate vital signs at least every 15 minutes



Consider (under medial direction):

Epinephrine 1:1000

• 0.3 mg (0.3 mL) IM into lateral thigh



Airway Threatened: Nebulized epinephrine 1:1000, 3–5 mL (3–5 mg)

Bronchospasm: Nebulized salbutamol 5 mg

(Wheeze or Hypoxia) Consider: Intubation / nebulized epinephrine

Hypotension: Place on cardiac monitor

(Systolic BP <100 mmHg) Further epinephrine 1:1000, 0.3 mg IM and

IV normal saline bolus 20 mL/kg STAT as needed

Have vasopressin on hand



Transfer to Emergency Room/ICU Observe until all symptoms resolved.

Table 9. Grading and Management of Allergic or Infusion-Related Reactions

Adverse	Grade					
Event	1	2	3	4	5	
Infusion- related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids): prophylactic medications indicated for ≤24 hours	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement, hospitalization indicated for clinical sequelae	Life- threatening consequences; urgent intervention required	Death	
Allergic reaction	Transient flushing or rash, drug fever <38.0°C. Intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids): prophylactic medications indicated for ≤24 hours	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement, hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates)	Life- threatening consequences; urgent intervention required	Death	
Anaphylaxis	_	_	Symptomatic bronchospasm, with or without urticarial; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life- threatening consequences; urgent intervention required	Death	
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids): prophylactic medications indicated for ≤24 hours	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement, hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates)	Life- threatening consequences; pressor or ventilator support indicated	Death	

Abstracted from NCI CTCAE Version 4.03.

10.3.3 Potential Immune Effects

An antibody blocking FcRn is anticipated to have several effects. These include acceleration of catabolism of IgG, but not other immunoglobulin isotypes such as IgA and IgM, leading to dose-dependent decreases in circulating IgG levels by up to an estimated 50% from the baseline levels after a single dose and further decreases after multiple doses up to a 70% to 80% reduction. Based on studies in humans, it is expected that with a single dose, the nadir of this effect will

occur approximately 5 days after dosing. The time course of recovery of IgG following dosing in the Phase 1a study suggests that a return to within 30% of baseline levels observed at pretreatment occurs within 4 weeks after a single dose and within 4 weeks after multiple doses as shown in NHPs.

Given the normal adult range of total IgG of 500 to 1600 mg/dL (Agarwal and Cunningham-Rundles, 2007; Furst, 2009; Gonzalez-Quintela et al., 2008; Jolliff et al., 1982; Keystone et al., 2007; McMillan et al., 1997; van Vollenhoven et al., 2013), with a mean of 1150 mg/dL, a 50% decrease in the mean would be to 575 mg/dL and a 50% decrease from the low end of the normal range used for the inclusion criteria of 600 mg/dL in this study would be to 300 mg/dL. An 80% decrease from baseline after multiple doses would result in IgG levels of 230 mg/dL and 120 mg/dL, respectively. While these levels are in the range found in patients with primary humoral immunodeficiency (Ameratunga et al., 2013), the levels will be transient. Further, as reported for other therapies used for pemphigus, the temporary (ie, less than 4 months) depletion of IgG (up to 95% reduction of total IgG as seen with immunoadsorption) does not appear to impart an increased risk of infection (Eming and Hertl, 2006; Furst, 2009; Keystone et al., 2007; Schmaldienst et al., 2001; van Vollenhoven et al., 2013). Study subjects will be monitored clinically for any infection. Further, commercial IVIG can be given to reverse the low IgG levels in case of a bacterial infection occurring while their IgG levels are decreased.

An antibody that blocks FcRn is expected to also down-modulate innate and adaptive immunity and the catabolism of IgG-containing immune complexes (IC). Specifically, it is expected that anti-FcRn will promote the clearance of IgG-containing ICs and the effects of these ICs on stimulating innate immune cell production of inflammatory cytokines (eg., interleukin 12 [IL-12], interferon-y, and tumor necrosis factor [TNF]) and inhibit the processing and presentation of antigens contained within ICs and thus the antigen-specific activation of CD4⁺ and CD8⁺ T-cells. Therefore, subjects with pre-existing conditions that are dependent upon IgG antibodies, such as chronic infections (eg, HIV, HBV or HCV), will be excluded from this study, as will subjects with active infection, in general.

Events of Special Interest 10.4

Not applicable.

10.5 **Other Safety Considerations**

10.5.1 **Laboratory Data**

All laboratory data obtained during the study should be reviewed. Any abnormal value that leads to a change in subject management (eg. requirement for additional medication or monitoring) or is determined to be of clinical significance by the Investigator should be reported as an AE and/or SAE as appropriate, unless this value is consistent with values obtained before entry into the study.

10.5.2 **Medication Errors**

Any medication error that results in an AE, even if it does not meet the definition of serious, requires reporting within 24 hours to the safety Medical Monitor. Refer to Section 10.2.3.2 for more information.

10.5.3 Overdose

For the purposes of this study, an overdose of SYNT001 is defined as a dose that is two-fold higher than the intended dose for the subject. As all dosing for this study will be conducted in a controlled clinical setting, an overdose is not anticipated. In the unlikely event an overdose should occur, it should be reported as an AE.

10.5.4 **Pregnancy**

If a female subject or the female partner of a male subject becomes pregnant during the course of the study, the Investigator must report the pregnancy to Medpace Safety using the **Pregnancy Reporting Form** within **24 hours** of becoming aware of the event. The Investigator must obtain consent to collect pregnancy information (including the status of the newborn, if applicable).

If some of the information required for completion of the Pregnancy Reporting Form is unavailable at the time of the initial report, follow-up reports will be completed and submitted within 24 hours of becoming aware of the new information. Any pregnancy will be followed through delivery for the observation of any SAEs. Any SAE that occurs during pregnancy must be recorded on the SAE report form in the EDC system (eg, maternal serious complications, therapeutic or spontaneous abortion, ectopic pregnancy, stillbirth, neonatal death, congenital abnormality, birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs (see Section 10.2.3.2).

11. STATISTICAL CONSIDERATIONS

11.1 General Design

This study is being conducted to evaluate the safety, tolerability, PK, PD, activity, and immunogenicity of SYNT001 in pemphigus patients.

11.2 Study Populations

Three populations will be employed in the analysis of study data:

- The **Safety** population will consist of all subjects who have received at least one dose of study drug.
- The **PD** population will consist of all subjects who receive at least one dose of study drug and have post-dose PD data available.
- The **PK** population will consist of all subjects who receive at least one dose of study drug and have post-dose PK data available.

Primary safety analyses will be performed on the safety population. Demographics, subject disposition, screening, and baseline characteristics will be summarized for the safety and PD/PK populations, where appropriate.

11.3 Sample Size Justification

Formal sample size calculations were not performed. The number of subjects was chosen based on feasibility and was considered sufficient to meet the study objectives.

11.4 Statistical Analysis

11.4.1 Statistical Analysis Plan

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP). The SAP may modify the plans outlined in the protocol; however, any deviations from the previously approved statistical plan will be described and justified in a SAP amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate and will be described in the SAP. The SAP including pharmacokinetic data analysis methodologies will be finalized prior to database lock.

All descriptive and inferential statistical analyses will be performed using Statistical Analysis System (SAS) version 9.4 or later. Missing data will not be imputed unless otherwise stated. All clinical data captured will be provided in data listings.

Methods of handling of missing data for different endpoints will be further specified in the SAP. In general, where individual data points are missing because of insufficient samples, dropouts, or other reasons, the data will be analyzed based on reduced denominators unless specified otherwise in the SAP.

11.4.2 Statistical Methodology

All clinical data captured will be provided in data listings. Subject disposition, demographic information, and baseline characteristics will be presented. Baseline will be defined at the last value obtained prior to the first dose of study drug. Results will be summarized by dose level and cohort. Any discrepancy between treatment to be given and treatment received will be accounted for in these displays.

Continuous data will be summarized using descriptive statistics: number of subjects (N), number of observations (n), mean, median, standard deviation (SD), minimum, and maximum.

Categorical data will be summarized using frequencies and percentages. When categorical data will be presented, the percent will be suppressed when the count is zero to draw attention to the non-zero counts. The denominator for all percentages, unless otherwise specified, will be the number of subjects in the specified analysis population.

11.4.3 Analysis of Primary Endpoints

11.4.3.1 Safety Data

All statistical analysis of safety outcomes will be descriptive. Safety observations and measurements include AEs, treatment-emergent AEs (TEAEs), SAEs, clinical safety laboratory tests, vital sign measurements, physical examinations, and ECGs. The incidence of AEs, TEAEs and SAEs will be summarized by cohort, severity and relationship to study product.

TEAEs will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA®; Version 19 or higher) System Organ Class (SOC) and preferred term, classified from verbatim terms. The incidence and percentage of subjects with at least one occurrence of a preferred term will be included, using the most severe grade. The number of events per preferred term will also be summarized. Causality (relationship to study treatment) will be summarized separately.

TEAEs, SAEs, and AEs leading to withdrawal, dose modification, or treatment discontinuation will be listed by subject, dose, and overall per SOC and preferred terms. Duration of AEs will be determined and included in listings, along with action taken and outcome.

Laboratory results will be summarized by cohort and time point. The incidence of laboratory abnormalities will be summarized. The worst on-study grade after the first dose of study drug will be summarized. Results for variables that are not coded will be presented in the listings as below, within, and above the normal limits of the local laboratory.

Vital sign measurements and change from baseline will be summarized at each scheduled time point by cohort using descriptive statistics.

Arithmetic mean of parameters from triplicate ECG will be calculated first for each subject at each planned time point. Then summary statistics of ECG test parameters (mean of triplicate) and change from baseline to each post-dose time point will be calculated. Shift tables for ECG test result category change (normal, abnormal, clinically abnormal) from pre-dose to each post-dose time point showing number and percentage of subjects with movement between categories

will be presented by treatment group. Frequency and percentage of subjects experiencing potential QTc prolongation (QTcF > 450) will be summarized at each time point by cohort.

Concomitant medications will be coded using WHO Drug Dictionary (WHO-DD March 2013, Type B2 or later) and the data will be summarized and presented in tables and listings.

11.4.3.2 Dose Selection Data

The evaluation of SYNT001 based on total IgG levels and responses on the PDAI total activity score from baseline will be summarized using descriptive statistics. Descriptive statistics will include mean, SD, coefficient of variation (CV), median, minimum, and maximum. The determination of dose and dosing duration of SYNT001 that achieves (i) total IgG level nadir decrease by \geq 60% and \leq 90% from baseline and (ii) a PDAI total activity score of \geq 50% reduction from baseline to allow further clinical development in subject with pemphigus (vulgaris or foliaceus).

11.4.4 Analysis of Secondary Endpoints

11.4.4.1 Pharmacokinetic Data

PK results for SYNT001 will be summarized by cohort and timepoint.

Study drug serum concentrations will be used to calculate the following PK parameters: t_{1/2}, C_{max}, T_{max}, and AUC₀₋₂₄ and AUC_{0-∞} in Cohort 1 and C_{max} for Cohorts 2, 3, and 4 (optional cohort). PK parameters will be determined using noncompartmental method(s). Descriptive statistics will be provided for the PK parameters including mean, SD, CV, median, minimum, and maximum. T_{max} will be reported as median and range. All descriptive statistics will be performed on untransformed PK parameters and after log₁₀ transformation of PK parameters.

For calculation of mean concentrations and generation of mean concentration-time profiles, all below the limit of quantification (BLQ) values will be set to zero except when an individual BLQ falls between 2 quantifiable values, in which case it will be omitted.

If there are values above the BLQ, but too sparse to allow full analysis, descriptive statistics will be performed on available values.

11.4.4.2 Pharmacodynamic/Activity Data

The evaluation of PD biomarkers will be based on absolute and percent change from baseline in serum levels of total IgG, IgG subtypes (IgG1-4), immunoglobulin A (IgA), immunoglobulin M (IgM), albumin, and CIC that will be summarized by cohort and timepoint.

11.4.4.3 Immunogenicity Data

Immunogenicity results will be summarized by cohort and timepoint. Descriptive statistics will include mean, SD, CV, median, minimum, and maximum.

11.4.4.4 PDAI Data

PDAI results will be summarized by score (total activity score, total damage score), cohort, and timepoint. Descriptive statistics will include absolute change from baseline, and percent change from baseline. PDAI will also be summarized by disease severity category, mild (0 to 8), moderate (9 to 24), and severe (≥25).

11.4.5 Analysis of Exploratory Endpoints

11.4.5.1 Corticosteroid Use

The evaluation of corticosteroid use during the study will be summarized by cohort and timepoint.

11.4.5.2 Health-Related Quality of Life Data

HR-QoL results from the ABQoL and Skindex-29 assessments will be summarized by cohort and timepoint

11.4.5.3 Photography

The qualitative assessment of changes in appearance of skin and mucosal lesions as determined by photography presented by cohort and timepoint.

11.5 Interim Analysis

No interim analysis is planned.

12. STUDY MANAGEMENT

12.1 Regulatory and Ethical Considerations

12.1.1 Ethical Conduct

The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH E6 Tripartite Guideline (January 1997), and in general, be conducted in a manner consistent with the principles described in the Declaration of Helsinki. The Investigator will ensure that the conduct of the study complies with the basic principles of GCP as outlined in the current version of 21 CFR, subpart D, Part 312, "Responsibilities of Sponsors and Investigators", Part 50, "Protection of Human Subjects", and Part 56, "Institutional Review Boards".

12.1.2 Informed Consent

A signed informed consent form (ICF) in compliance with 21 CFR, Part 50.25(a) and Part 50.25(b) and the ICH guidelines, will be obtained from each subject before the subject is entered into the study and before any study screening procedure is performed that involves risk. The method of obtaining and documenting the informed consent will comply with ICH GCP and all applicable laws and regulations and will be subject to approval by the Sponsor.

The Investigator, or designee, is responsible for obtaining written informed consent from each subject (or the subject's legally authorized representative) participating in this study after a thorough and clear explanation of the objectives, procedures, anticipated benefits, and potential hazards of the study. In the case where the subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the subject has orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. The study site must retain the original ICF and a copy must be provided to the subject or to the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

The Sponsor, or designee, must review the signed ICF against any proposed deviations from a sample ICF the Sponsor has supplied to each site. The final IRB-approved document must be provided to the Sponsor for regulatory purposes.

The eCRF for this study contains a section for documenting informed subject consent, and this must be completed appropriately. Signed ICFs must remain in each subject's study file and must be available for verification by site monitors at any time. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated as necessary. All subjects (including those already being treated) should be informed of the new information, should be given a copy of the revised form, and should give their consent to continue in the study.

12.1.3 Subject Confidentiality and Privacy

As applicable, in accordance with the Health Insurance Portability and Accountability Act (HIPAA), and associated privacy regulations, a patient authorization to use personally

identifiable health information may be required from each patient before research activities begin.

The Investigator must ensure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On eCRFs or other documents submitted to the Sponsor, subjects should be identified by an identification code and not by their names. The Investigator should keep a subject enrollment log showing codes, names, and addresses. The Investigator should maintain documents intended for storing onsite (eg, subjects' written consent forms) in strict confidence.

All study drugs, subject bodily fluids and tissue, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the Sponsor.

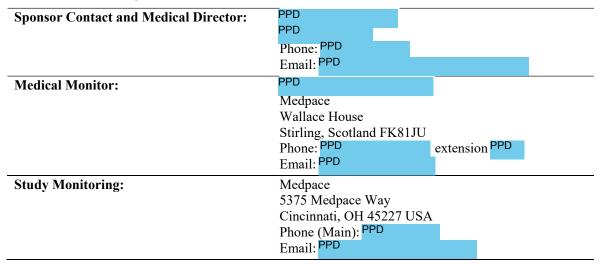
12.1.4 Future Use of Stored Specimens

Not all the tissue and blood components obtained during this study may be required for the tests that are part of the clinical trial. Available samples may be used for additional research. This research will help to understand disease subtypes, drug response, and AEs, and possibly identify new drug targets or biomarkers that predict subject response to treatment. The use of the samples for internal research will adhere to the guidelines defined by the FDA in "Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individual Identifiable" (issued 25 April 2006) and the European Medicines Agency (EMA) "Reflection Paper on Pharmacogenetic Samples, Testing and Data Handling" (Doc. Ref. EMEA/CHMP/PGxWP/201914/2006; 15 November 2007). If a subject requests destruction of their tissue and blood samples and the samples have not yet been de-identified, the Sponsor will destroy the samples as described in the FDA guidance. The Sponsor will notify the Investigator in writing that the samples have been destroyed.

12.2 Study Administration

The study administration structure is provided in Table 10.





12.2.1 Institutional Review Board Approval

This study is being conducted under US IND 132727. This protocol (and any modifications) and appropriate consent procedures must be reviewed and approved by the site-specific IRB before the study is initiated. The IRB must operate in accordance with the current federal or local regulations. The Investigator will send a letter or certificate of IRB approval to the Sponsor (or designee) before subject enrollment and whenever subsequent modifications to the protocol are made.

12.2.2 Data Handling and Record Keeping

All data will be entered in a validated electronic data capture system using single data entry. Standard procedures (including following data review guidelines, manual clinical review based on subject profiles, computerized validation to produce queries, and maintenance of an audit file, which includes all database modifications) will be followed to ensure accurate data. Clinical personnel will review all data listings for outliers, data inconsistencies, and spelling errors.

12.2.3 Data Protection

The Investigator agrees that all information received from the Sponsor, including but not limited to the IB, this protocol, eCRFs, the INDs, and any other study information remain the sole and exclusive property of the Sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) or otherwise into the public domain without prior written consent from the Sponsor.

12.2.4 Study Site Regulatory Documentation

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should

be classified into 2 separate categories as follows: (1) Investigator's study file and (2) subject clinical source documents (see Section 12.2.5).

The Investigator's study file will contain the protocol and protocol amendments, eCRFs, query forms, IRB and governmental approval with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Subject clinical source documents (usually predefined by the project to record key efficacy and safety parameters independent of the eCRFs) may include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalogram, X-ray, pathology and special assessment reports, signed ICFs, consultant letters, and subject screening and enrollment logs. The Investigator must keep these two categories of documents on file for at least 2 years following the marketing application approval date for the study treatment and for the indication being investigated or for 2 years after the development program is discontinued and the FDA notified. After that period, the documents may be destroyed subject to local regulations with prior written permission from the Sponsor. If the Investigator wants to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

If the Investigator cannot guarantee the archiving requirement at the study site for any or all of the documents, special arrangements must be made between the Investigator and the Sponsor to store these in a sealed container outside of the study site so that they can be returned sealed to the Investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the study site.

12.2.5 Subject Clinical Source Documents and Background Data

Investigators must maintain adequate and accurate source documents on which the eCRFs for each subject are based. They are separate and distinct from the eCRFs.

These records include detailed notes on the following:

- Medical history
- Informed consent
- HIPAA authorization, if applicable (either contained in the ICF or presented to the subject candidate as a standalone document)
- Description of the complete consenting process
- The basic identifying information that linked the subject's medical record with the eCRFs
- The results of all diagnostic tests performed, diagnoses made, therapy provided, and any other data on the condition of the subject
- The medical condition of the subject during their involvement in the study
- All AEs
- The subject's exposure to the study medication
- The subject's exposure to any concomitant therapy
- All relevant observations and data on the condition of the subject throughout the trial
- Justification for all entries in the subject's eCRF

A subject log of all potentially eligible subjects considered, but not consented, for obvious deviations from the entry criteria, will be kept at each site. The log will contain subjects' initials, diagnosis, eligibility, or, if not eligible, reason for not consenting. All consented subjects will be logged, regardless of whether they ultimately enroll.

Upon request, the Investigator will supply the Sponsor with any required background data from the study documentation or clinic records. This is particularly important when eCRFs are illegible or when errors in data transcription are suspected. In case of special problems or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

12.2.6 Electronic Case Report Forms

Clinical trial data for this study will be captured on eCRF designed for computer processing and analysis. This computerized system will be validated and compliant with 21 CFR Part 11, as described in the FDA guidance "Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11 – Questions and Answers." If corrections are made after review and sign-off by the Investigator, he/she must be aware of the changes and provide written acknowledgement. There will also be an electronic audit trail. Corrections on paper CRFs must be initialed and dated by the person making the change. The Investigator agrees to provide all information requested on the eCRF in an accurate manner using instructions provided. The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to Syntimmune in the eCRF and in all required reports.

An eCRF is required to be submitted for every subject who receives any amount of study drug. This includes submission of retrievable data on subjects who withdraw before completion of the study. Prior to submission, eCRFs must be reviewed for completeness and accuracy, and signed and dated where indicated, by the Investigator or designee. If a subject stops treatment or terminates from the study, the dates and reasons must be noted on the eCRF.

12.3 Clinical Monitoring, Audits, and Inspections

The Investigator and study staff are responsible for maintaining a comprehensive and accurate filing system of all study-related documentation that will be suitable for inspection for routine monitoring, audit, or inspection at any time by the Sponsor (or designee) and/or a regulatory authority.

12.3.1 Clinical Monitoring

During the clinical study, it is understood that the responsible Sponsor site monitor or designee (eg, contract research organization [CRO]) will contact and visit the study site at regular intervals for routine monitoring of various records. Routine monitoring activities will be conducted to verify adherence to the protocol, completeness, consistency and accuracy of the data, and to review study source documents and drug accountability records. Regular review of the eCRFs for completeness, clarity, and to cross-check against source documents is required to

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monitor the progress of the study. Data will be reviewed and verified against the source documents (eg, original medical records and laboratory results) to ensure validity.

The Investigator will provide the Sponsor or designee with full access to all source data (including laboratory tests) and provide administrative support if requested. The Investigator (or designee) must agree to cooperate with the site monitor to ensure that any problems detected during these monitoring visits are resolved.

Site-specific study procedures, such data-recording and handling of the data, may be assessed during the study by a Clinical Quality Assurance representative(s) authorized by the Sponsor. Further, this designee, as well as the site monitor, will be permitted to inspect the study documents (study protocol, eCRFs, study drug accountability, original study-relevant medical records) to ensure that the study is conducted in compliance with the protocol.

During these visits, all representatives of the Sponsor will be responsible for ensuring data integrity and subject confidentiality is protected.

12.3.2 Audits and Inspections

Clinical site and study audits will be conducted as necessary to assure the validity of the study data. The Sponsor (or designee) may perform a quality assurance audit to ensure compliance with GCP, this protocol, and all applicable regulatory requirements. The Investigator should ensure that study documents (protocol, eCRFs, study drug record-keeping, original study-relevant medical records) are made available to the Sponsor (or designee) for examination. All subject data will be treated as confidential.

A regulatory authority, after appropriate notification, may also wish to conduct an inspection during the study or even after its completion. If a regulatory authority requests an inspection, the Investigator must immediately inform the Sponsor.

12.4 Changes to the Protocol

Protocol modifications to ongoing studies must be made only after consultation between a Sponsor representative and the Investigator. Protocol modifications will be prepared, reviewed, and approved by Sponsor representatives.

All protocol modifications must be submitted to the IRB for information and approval in accordance with local requirements, and to regulatory agencies, if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study subjects, or when the change involves only logistical or administrative aspects of the trial (eg, change in site monitor, change of telephone number).

12.5 Study Discontinuation and Closure

The Sponsor has the right to terminate the study at any time. In terminating the study, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the subjects' interests.

13. PUBLICATION AND DATA SHARING POLICY

The results of this study may be published or presented at scientific meetings. The Investigator agrees that any manuscript or abstract they author may be published only after receiving written permission from the Sponsor.

If the Sponsor coordinates a publication or presentation of study results from all study sites, the participation of Investigator or other representatives of study site as a named author shall be determined in accordance with the Sponsor's policy and generally accepted standards for authorship as developed by the International Committee of Medical Journal Editors (ICMJE) and in accordance with Good Publication Practices.

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APPENDIX 1. NCI CTCAE, VERSION 4.03

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Common Terminology Criteria for Adverse Events (CTCAE)

Version 4.0

Published: May 28, 2009 (v4.03: June 14, 2010)

U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health National Cancer Institute

Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

Quick Reference

The NCI Common Terminology Criteria Adverse Events is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

SOC

System Organ Class, the highest level of the MedDRA hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e. SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

CTCAE Terms

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disea temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analysis Each CTCAE v4.0 term is a MedDRA LLT (Lowest Level Term).

Publish Date: May 28, 2009

Definitions

A brief definition is provided to clarify the meaning of each AE term.

Grades

displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic telephone, managing money, etc. observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; medications, and not bedridden. limiting age-appropriate instrumental ADL*.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

A Semi-colon indicates 'or' within the description of the grade.

A single dash (-) indicates a grade is not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than e options for Grade selection.

Grade refers to the severity of the AE. The CTCAE Grade 5 (Death) is not appropriate for some AEs displays Grades 1 through 5 with unique clinical and therefore is not an option.

ctivities of Daily Living (ADL)

- Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the
- Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking

[†] CTCAE v4.0 incorporates certain elements of the MeduRA terminology. For further details on MedDRA refer to the MedDRA MSSO Web site (http://www.meddramsso.com).

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	В	lood and lymphatic system	em disorders		
			Grade		
Adverse Event	1 2		3	4	5
Anemia	Hemoglobin (Hgb) <lln -="" 10.0<br="">g/dL; <lln -="" -<br="" 6.2="" <lln="" l;="" mmol="">100 g/L</lln></lln>	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
	ed by an reduction in the amount of palpitations of the heart, soft syst	•	• • •	ay include pallor of the skin and m	nucous
Bone marrow hypocellular	Mildly hypocellular or <=25% reduction from normal cellularity for age	Moderately hypocellular or >25 - <50% reduction from normal cellularity for age	Severely hypocellular or >50 - <=75% reduction cellularity from normal for age	Aplastic persistent for longer than 2 weeks	Death
Definition: A disorder characteriz	ed by the inability of the bone mar	row to produce hematopoietic ele	ments.		
Disseminated intravascular coagulation	-	Laboratory findings with no bleeding	Laboratory findings and bleeding	Life-threatening consequences; urgent intervention indicated	Death
	ed by systemic pathological activa s depleted of platelets and coagula	-	which results in clot formation thro	oughout the body. There is an incr	ease in the
Febrile neutropenia	-	-	ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour.	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz degrees F) for more than one ho	ed by an ANC <1000/mm3 and a sur.	single temperature of >38.3 degre	es C (101 degrees F) or a sustaine	ed temperature of >=38 degrees 0	C (100.4
Hemolysis	Laboratory evidence of hemolysis only (e.g., direct antiglobulin test; DAT; Coombs'; schistocytes; decreased haptoglobin)	Evidence of hemolysis and >=2 gm decrease in hemoglobin.	Transfusion or medical intervention indicated (e.g., steroids)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by laboratory test results that in	ndicate widespread erythrocyte ce	Il membrane destruction.	I	
Hemolytic uremic syndrome	Evidence of RBC destruction (schistocytosis) without clinical consequences	-	Laboratory findings with clinical consequences (e.g., renal insufficiency, petechiae)	Life-threatening consequences, (e.g., CNS hemorrhage or thrombosis/embolism or renal failure)	Death
Definition: A disorder characteriz	ed by a form of thrombotic microa	ngiopathy with renal failure, hemo	lytic anemia, and severe thromboo	ytopenia.	
_eukocytosis	-	-	>100,000/mm3	Clinical manifestations of leucostasis; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by laboratory test results that ir	ndicate an increased number of w	nite blood cells in the blood.		
_ymph node pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by a sensation of marked disco	omfort in a lymph node.			
Spleen disorder	Incidental findings (e.g., Howell- Jolly bodies); mild degree of thrombocytosis and leukocytosis	Prophylactic antibiotics indicated	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder of the splee	en.				
Thrombotic thrombocytopenic ourpura	Evidence of RBC destruction (schistocytosis) without clinical consequences	-	Laboratory findings with clinical consequences (e.g., renal insufficiency, petechiae)	Life-threatening consequences, (e.g., CNS hemorrhage or thrombosis/embolism or renal failure)	Death
	ed by the presence of microangion al disturbances. It is an acute or s	•	cytopenic purpura, fever, renal abr	normalities and neurological abnor	malities suc
Blood and lymphatic system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic	Moderate; minimal, local or noninvasive intervention	Severe or medically significant but not immediately life-	Life-threatening consequences; urgent intervention indicated	Death
	observations only; intervention not indicated	indicated; limiting age- appropriate instrumental ADL	threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL		

		Cardiac disorde	:15				
	Grade						
Adverse Event	1	2	3	4	5		
Acute coronary syndrome	-	Symptomatic, progressive angina; cardiac enzymes normal; hemodynamically stable	Symptomatic, unstable angina and/or acute myocardial infarction, cardiac enzymes abnormal, hemodynamically stable	Symptomatic, unstable angina and/or acute myocardial infarction, cardiac enzymes abnormal, hemodynamically unstable	Death		
	ed by signs and symptoms related unstable angina to myocardial infa	I to acute ischemia of the myocard arction.	lium secondary to coronary artery	disease. The clinical presentation	covers a		
Aortic valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis by imaging	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death		
Definition: A disorder characterize	ed by a defect in aortic valve funct	tion or structure.	,				
Asystole	Periods of asystole; non-urgent medical management indicated			Life-threatening consequences; urgent intervention indicated	Death		
		ac electrical activity. Typically, this			.		
Atrial fibrillation	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker), or ablation	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characterize originates above the ventricles.	ed by a dysrhythmia without disce	rnible P waves and an irregular ve	entricular response due to multiple	reentry circuits. The rhythm distur	bance		
Atrial flutter	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker), or ablation	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characterize atria.	ed by a dysrhythmia with organize	ed rhythmic atrial contractions with	a rate of 200-300 beats per minut	e. The rhythm disturbance origina	tes in the		
Atrioventricular block complete	-	Non-urgent intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characterize	· ed by a dysrhythmia with complete	e failure of atrial electrical impulse	conduction through the AV node	to the ventricles.	•		
Atrioventricular block first degree	Asymptomatic, intervention not indicated	Non-urgent intervention indicated	-	-	-		
	ed by a dysrhythmia with a delay i interval greater than 200 milliseco	n the time required for the conducted ands.	tion of an electrical impulse throuç	gh the atrioventricular (AV) node b	eyond 0.2		
Cardiac arrest	-	-	-	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characterize	ed by cessation of the pumping fu	nction of the heart.	<u> </u>	<u> </u>			
Chest pain - cardiac	Mild pain	Moderate pain; limiting instrumental ADL	Pain at rest; limiting self care ADL	-	-		
Definition: A disorder characterize	ed by substernal discomfort due to	insufficient myocardial oxygenati	on.				
Conduction disorder	Mild symptoms; intervention not indicated	Moderate symptoms	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characterize	ed by pathological irregularities in	the cardiac conduction system.					
Constrictive pericarditis	-	-	Symptomatic heart failure or other cardiac symptoms, responsive to intervention	Refractory heart failure or other poorly controlled cardiac symptoms	Death		
Definition: A disorder characterize	ed by a thickened and fibrotic peri	cardial sac; these fibrotic changes		1	e action.		
Heart failure	Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic	Death		

		Cardiac disorde				
			Grade			
Adverse Event	1	2	3	4	5	
_eft ventricular systolic dysfunction	-	-	Symptomatic due to drop in ejection fraction responsive to intervention	Refractory or poorly controlled heart failure due to drop in ejection fraction; intervention such as ventricular assist device, intravenous vasopressor support, or heart transplant indicated	Death	
	zed by failure of the left ventricle to nea, orthopnea, and other signs ar			e and in end-diastolic volume. Clin	ical	
Mitral valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis by imaging	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death	
Definition: A disorder characteriz	red by a defect in mitral valve func	tion or structure.		_		
Mobitz (type) II atrioventricular olock	Asymptomatic, intervention not indicated	Symptomatic; medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening consequences; urgent intervention indicated	Death	
	zed by a dysrhythmia with relatively atrioventricular (AV) node to the ve	•	block of an atrial impulse. This is t	he result of intermittent failure of a	trial elect	
Mobitz type I	Asymptomatic, intervention not indicated	Symptomatic; medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening consequences; urgent intervention indicated	Death	
	ed by a dysrhythmia with a progre on through the atrioventricular (AV		ior to the blocking of an atrial impu	alse. This is the result of intermitter	nt failure o	
Myocardial infarction	-	Asymptomatic and cardiac enzymes minimally abnormal and no evidence of ischemic ECG changes	Severe symptoms; cardiac enzymes abnormal; hemodynamically stable; ECG changes consistent with infarction	Life-threatening consequences; hemodynamically unstable	Death	
Definition: A disorder characteriz	ed by gross necrosis of the myoca	ardium; this is due to an interruption	on of blood supply to the area.			
Myocarditis	Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	Death	
Definition: A disorder characteriz	red by inflammation of the muscle	1	1	1		
Palpitations	Mild symptoms; intervention not indicated	Intervention indicated	-	-	-	
Definition: A disorder characteriz	red by an unpleasant sensation of		f the heart.	T		
Paroxysmal atrial tachycardia	Asymptomatic, intervention not indicated	Symptomatic; medical management indicated	IV medication indicated	Life-threatening consequences; incompletely controlled medically; cardioversion indicated	Death	
Definition: A disorder characteriz originates in the atria.	red by a dysrhythmia with abrupt o	nset and sudden termination of at	rial contractions with a rate of 150	-250 beats per minute. The rhythm	disturba	
Pericardial effusion	-	Asymptomatic effusion size small to moderate	Effusion with physiologic consequences	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characteriz	red by fluid collection within the pe	ricardial sac, usually due to inflam	nmation.		,	
Pericardial tamponade	-	-	-	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characteriz	red by an increase in intrapericardi	al pressure due to the collection of	of blood or fluid in the pericardium.	1		
	i .	Symptomatic pericarditis (e.g.,	Pericarditis with physiologic	Life-threatening consequences;	Death	

		Cardiac disorde	ers		
			Grade		
Adverse Event	1	2	3	4	5
Pulmonary valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis by imaging	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death
Definition: A disorder characteriz	ed by a defect in pulmonary valve	function or structure.	i	i	1
Restrictive cardiomyopathy	-	-	Symptomatic heart failure or other cardiac symptoms, responsive to intervention	Refractory heart failure or other poorly controlled cardiac symptoms	Death
	red by an inability of the ventricles	1	T ,	1	
Right ventricular dysfunction	Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Severe symptoms, associated with hypoxemia, right heart failure; oxygen indicated	Life-threatening consequences; urgent intervention indicated (e.g., ventricular assist device); heart transplant indicated	Death
	ed by impairment of right ventricul				
Sick sinus syndrome	Asymptomatic, intervention not indicated	Non-urgent intervention indicated	Severe, medically significant; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	ed by a dysrhythmia with alternation			1	1
Sinus bradycardia	Asymptomatic, intervention not indicated	Symptomatic, medical intervention indicated	Severe, medically significant, medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by a dysrhythmia with a heart r	ate less than 60 beats per minute	that originates in the sinus node.	T	1
Sinus tachycardia	Asymptomatic, intervention not indicated	Symptomatic; non-urgent medical intervention indicated	Urgent medical intervention indicated	-	-
Definition: A disorder characteriz	ed by a dysrhythmia with a heart r	ate greater than 100 beats per mi	nute that originates in the sinus no	de.	
Supraventricular tachycardia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by a dysrhythmia with a heart r	ate greater than 100 beats per mi	nute that originates above the ven	tricles.	
Tricuspid valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death
Definition: A disorder characteriz	ed by a defect in tricuspid valve fu	nction or structure.			
Ventricular arrhythmia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by a dysrhythmia that originate	s in the ventricles.			
Ventricular fibrillation	-	-	-	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Definition: A disorder characteriz ventricles.	ed by a dysrhythmia without disce	rnible QRS complexes due to rapi	d repetitive excitation of myocardi	al fibers without coordinated contr	action of the
Ventricular tachycardia	-	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by a dysrhythmia with a heart r	ate greater than 100 beats per mi	nute that originates distal to the bu	indle of His.	
Wolff-Parkinson-White syndrome	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with procedure	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by the presence of an accesso	ry conductive pathway between th	e atria and the ventricles that caus	ses premature ventricular activation	n.
Cardiac disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

	Congenital, familial and genetic disorders					
Grade						
Adverse Event	1	2	3	4	5	
Congenital, familial and genetic disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	

		Ear and labyrinth dis	orders		
			Grade		
Adverse Event	1	2	3	4	5
Ear pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by a sensation of marked disco	omfort in the ear.			
External ear inflammation	External otitis with erythema or dry desquamation	External otitis with moist desquamation, edema, enhanced cerumen or discharge; tympanic membrane perforation; tympanostomy	External otitis with mastoiditis; stenosis or osteomyelitis; necrosis of soft tissue or bone	Urgent operative intervention indicated	Death
Definition: A disorder characteriz	ed by inflammation, swelling and r	edness to the outer ear and ear ca	anal.		
External ear pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by a sensation of marked disco	mfort in the external ear region.		.	
Hearing impaired	Adults enrolled on a Monitoring Program (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift of 15 - 25 dB averaged at 2 contiguous test frequencies in at least one ear. Adults not enrolled in Monitoring Program: subjective change in hearing in the absence of documented hearing loss. Pediatric (on a 1, 2, 3, 4, 6 and	Adults enrolled in Monitoring Program (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift of >25 dB averaged at 2 contiguous test frequencies in at least one ear. Adults not enrolled in Monitoring Program: hearing loss but hearing aid or intervention not indicated; limiting instrumental ADL.	Adults enrolled in Monitoring Program (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift of >25 dB averaged at 3 contiguous test frequencies in at least one ear; therapeutic intervention indicated. Adults not enrolled in Monitoring Program: hearing loss with hearing aid or intervention indicated; limiting self care ADL.	Adults: Decrease in hearing to profound bilateral loss (absolute threshold >80 dB HL at 2 kHz and above); non-servicable hearing. Pediatric: Audiologic indication for cochlear implant and additional speech-language related services indicated.	-
	8 kHz audiogram): Threshold shift >20 dB at 8 kHz in at least one ear.	Pediatric (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift >20 dB at 4 kHz and above in at least one ear.	Pediatric (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): hearing loss sufficient to indicate therapeutic intervention, including hearing aids; threshold shift >20 dB at 3 kHz and above in at least one ear; additional speech-language related services indicated.		
	red by partial or complete loss of the				
Middle ear inflammation	Serous otitis	Serous otitis, medical intervention indicated	Mastoiditis; necrosis of canal soft tissue or bone	Life-threatening consequences; urgent intervention indicated	Death
	red by inflammation (physiologic re	i i			
Tinnitus	Mild symptoms; intervention not indicated	instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Vertigo	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characteriz vertigo).	eed by a sensation as if the externa	1	ı	I he himself were revolving in space	e (subjective
Vestibular disorder	-	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by dizziness, imbalance, nause	ea, and vision problems.			
Ear and labyrinth disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Endocrine disorders							
			Grade				
Adverse Event	1	2	3	4	5		
Adrenal insufficiency	Asymptomatic; clinical or diagnostic observations only; intervention not indicated as when the adrenal cortex does not	Moderate symptoms; medical intervention indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death		
	son's disease or primary adrenal in:	· -	cortisor and in some cases, the no	innone aldosterone. It may be due	to a disord		
Cushingoid	Mild symptoms; intervention not indicated		Severe symptoms, medical intervention or hospitalization indicated	-	-		
Definition: A disorder characteriosteoporosis, usually due to exc	ized by signs and symptoms that re ogenous corticosteroids.	semble Cushing's disease or synd	drome: buffalo hump obesity, striat	ions, adiposity, hypertension, diab	etes, and		
Delayed puberty	-	No breast development by age 13 yrs for females; testes volume of <3 cc or no Tanner Stage 2 development by age 14.5 yrs for males	No breast development by age 14 yrs for females; no increase in testes volume or no Tanner Stage 2 by age 16 yrs for males; hormone replacement indicated	-	-		
Definition: A disorder characteri	ized by unusually late sexual matur	ity.	'	'			
Growth accelerated	-	>= +2 SD (standard deviation) above mid parental height or target height	-	-	-		
Definition: A disorder characteri	zed by greater growth than expecte	ed for age.	1	1	1		
Hyperparathyroidism	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-		
Definition: A disorder characteri the blood).	ized by an increase in production of	parathyroid hormone by the para	thyroid glands. This results in hype	ercalcemia (abnormally high levels	of calcium		
Hyperthyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteri	zed by excessive levels of thyroid h	normone in the body. Common ca	uses include an overactive thyroid	gland or thyroid hormone overdos	se.		
Hypoparathyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; medical intervention or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteri	zed by a decrease in production of	parathyroid hormone by the parat	hyroid glands.				
Hypothyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid replacement indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death		
	zed by a decrease in production of		and.		1		
Precocious puberty	Physical signs of puberty with no biochemical markers for females <8 years and males <9 years	Physical signs and biochemical markers of puberty for females <8 years and males <9 years	-	-	-		
Definition: A disorder characteri 9 for boys.	ized by unusually early developmer	nt of secondary sexual features; th	e onset of sexual maturation begin	ns usually before age 8 for girls an	d before ag		
/irilization	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-		
Definition: A disorder characteri	ized by inappropriate masculinizatio	on occurring in a female or prepub	ertal male.	_			
Endocrine disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated;	Life-threatening consequences; urgent intervention indicated	Death		

		Eye dis	sorders		
			Grade		
Adverse Event	1	2	3	4	5
Blurred vision	Intervention not indicated	Symptomatic; limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder charact	erized by visual perception of u		<u> </u>	<u> </u>	ĺ
Cataract	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; moderate decrease in visual acuity (20/40 or better)	Symptomatic with marked decrease in visual acuity (worse than 20/40 but better than 20/200); operative intervention indicated (e.g.,	Blindness (20/200 or worse) in the affected eye	-
	<u> </u>		cataract surgery)		
Definition: A disorder charact untreated.	erized by partial or complete op	acity of the crystalline lens of c	one or both eyes. This results in	n a decrease in visual acuity an	d eventual blindness if
Conjunctivitis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; topical intervention indicated (e.g., antibiotics); limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder charact	erized by inflammation, swelling	and redness to the conjunctive	a of the eye.	1	I
Corneal ulcer	-	Symptomatic; medical intervention indicated (e.g., topical agents); limiting instrumental ADL	Limiting self care ADL; declining vision (worse than 20/40 but better than 20/200)	Perforation or blindness (20/200 or worse) in the affected eye	-
Definition: A disorder charact	erized by an area of epithelial ti	ssue loss on the surface of the	cornea. It is associated with in	flammatory cells in the cornea	and anterior chamber.
Dry eye	Asymptomatic; clinical or diagnostic observations only; mild symptoms relieved by lubricants	Symptomatic; multiple agents indicated; limiting instrumental ADL	Decrease in visual acuity (<20/40); limiting self care ADL	-	-
Definition: A disorder charact	erized by dryness of the cornea	and conjunctiva.			
Extraocular muscle paresis	Asymptomatic; clinical or diagnostic observations only	Symptomatic; limiting instrumental ADL	Limiting self care ADL; disabling	-	-
Definition: A disorder charact	erized by incomplete paralysis	of an extraocular muscle.	T	T	
Eye pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder charact	erized by a sensation of marked	d discomfort in the eye.		ı	1
Eyelid function disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; nonoperative intervention indicated; limiting instrumental ADL	Limiting self care ADL; operative intervention indicated	-	-
Definition: A disorder charact	erized by impaired eyelid function	on.	T	Т	T
Flashing lights	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder charact	erized by a sudden or brief burs	st of light.			
Floaters	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder charact	erized by an individual seeing s	pots before their eyes. The spo	ots are shadows of opaque cell	fragments in the vitreous humo	or or lens.
Glaucoma	Elevated intraocular pressure (EIOP) with single topical agent for intervention; no visual field deficit	EIOP causing early visual field deficits; multiple topical or oral agents indicated; limiting instrumental ADL	EIOP causing marked visual field deficits (e.g., involving both superior and inferior visual fields); operative intervention indicated; limiting self care ADL	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder charact	erized by an increase in pressu	· re in the eyeball due to obstruc	tion of the aqueous humor out	flow.	:
Keratitis	-	Symptomatic; medical intervention indicated (e.g., topical agents); limiting instrumental ADL	Decline in vision (worse than 20/40 but better than 20/200); limiting self care ADL	Perforation or blindness (20/200 or worse) in the affected eye	-
Definition: A disorder charact	erized by inflammation to the co	ornea of the eye.	T	T	
Night blindness	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder charact	erized by an inability to see clea	arly in dim light.			

		Eye dis	sorders		
			Grade		
Adverse Event	1	2	3	4	5
Optic nerve disorder	Asymptomatic; clinical or diagnostic observations only	Limiting vision of the affected eye (20/40 or better)	Limiting vision in the affected eye (worse than 20/40 but better than 20/200)	Blindness (20/200 or worse) in the affected eye	-
	erized by involvement of the op	1	ĺ		1
Papilledema	Asymptomatic; no visual field defects	vision; visual field defect present sparing the central 20 degrees	Marked visual field defect (worse than 20/40 but better than 20/200)	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder charact	erized by swelling around the o	ptic disc. T	<u> </u>	<u> </u>	
Photophobia	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder charact	erized by fear and avoidance of	f light.			
Retinal detachment	Asymptomatic	Exudative and visual acuity 20/40 or better	Rhegmatogenous or exudative detachment; operative intervention indicated; decline in vision (worse than 20/40 but better than 20/200)	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder charact	erized by the separation of the	inner retina layers from the und	lerlying pigment epithelium.		
Retinal tear	-	Laser therapy or pneumopexy indicated	Vitroretinal surgical repair indicated	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder charact	erized by a small laceration of t	he retina, this occurs when the	vitreous separates from the re	tina. Symptoms include flashes	s and floaters.
Retinal vascular disorder	-	Topical medication indicated	Intravitreal medication; operative intervention indicated	-	-
Definition: A disorder charact	erized by pathological retinal bl	ood vessels that adversely affe	cts vision.		
Retinopathy	Asymptomatic; clinical or diagnostic observations only	Symptomatic with moderate decrease in visual acuity (20/40 or better); limiting instrumental ADL	Symptomatic with marked decrease in visual acuity (worse than 20/40); disabling; limiting self care ADL	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder involvin	g the retina.				
Scleral disorder	Asymptomatic; clinical or diagnostic observations only	Symptomatic, limiting instrumental ADL; moderate decrease in visual acuity (20/40 or better)	Symptomatic, limiting self care ADL; marked decrease in visual acuity (worse than 20/40)	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder charact	erized by involvement of the so	lera of the eye.	Τ	Τ	I
Uveitis	Asymptomatic; clinical or diagnostic observations only	•	Posterior or pan-uveitis	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder charact	erized by inflammation to the uv	vea of the eye.	i -	i -	1
Vitreous hemorrhage	Asymptomatic or mild symptoms; clinical or diagnostic observations only	Symptomatic; limiting instrumental ADL	Limiting self care ADL; vitrectomy indicated	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder charact	erized by blood extravasation in	nto the vitreous humor.	T	T	T
Watering eyes	Intervention not indicated	Intervention indicated	Operative intervention indicated	-	-
Definition: A disorder of exce	ssive tearing in the eyes; it can	be caused by overproduction of	of tears or impaired drainage of	the tear duct.	
Eye disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately sight- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye	-

		Gastrointestinal dis	orders				
	Grade						
Adverse Event	1	2	3	4	5		
Abdominal distension	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe discomfort; limiting self care ADL	-	-		
Definition: A disorder characte	erized by swelling of the abdomen.				1		
Abdominal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-		
Definition: A disorder characte	erized by a sensation of marked disco	omfort in the abdominal region.	T	Г	1		
Anal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characte	erized by an abnormal communication	between the opening in the anal	canal to the perianal skin.				
Anal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characte	erized by bleeding from the anal region	on.	T		1		
Anal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characte	erized by inflammation of the mucous	membrane of the anus.	T	<u> </u>	1		
Anal necrosis	-	a in the engl region	TPN or hospitalization indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
	erized by a necrotic process occurring		Sovere pain: limiting self core				
Anal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-		
	erized by a sensation of marked disco		0 1 1 1	Let up a control of the control of t	Б. "		
Anal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Symptomatic and severely altered GI function; non- emergent operative intervention indicated; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder characte	erized by a narrowing of the lumen of	the anal canal.					
Anal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder characte	erized by a circumscribed, inflammato	ory and necrotic erosive lesion on t	the mucosal surface of the anal ca	nal.			
Ascites	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder characte	erized by accumulation of serous or h	emorrhagic fluid in the peritoneal	cavity.	•	•		
Bloating	No change in bowel function or oral intake	Symptomatic, decreased oral intake; change in bowel function	-	-	-		
Definition: A disorder characte	rized by subject-reported feeling of ι	uncomfortable fullness of the abdo	men.	•	•		
Cecal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characte	erized by bleeding from the cecum.			•	•		
Cheilitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; intervention indicated	-	-		
		1	I .	ı	I		

Gastrointestinal disorders Grade							
Adverse Event				4			
Colitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characte	rized by inflammation of the colon.		·				
Colonic fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; bowel rest, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characte	rized by an abnormal communication	between the large intestine and	another organ or anatomic site.				
Colonic hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characte	rized by bleeding from the colon.	Г	T	Г			
Colonic obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated rized by blockage of the normal flow	Symptomatic; altered GI function	Hospitalization indicated; elective operative intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death		
	Tized by blockage of the normal flow			1 if_ 4l4i	D41-		
Colonic perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
	rized by a rupture in the colonic wall.	<u> </u>			ı		
Colonic stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder characte	rized by a narrowing of the lumen of	the colon.	'	'			
Colonic ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder characte	rized by a circumscribed, inflammato	ry and necrotic erosive lesion on	the mucosal surface of the colon.				
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL	Obstipation with manual evacuation indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characte	rized by irregular and infrequent or d	ifficult evacuation of the bowels.					
Dental caries	One or more dental caries, not involving the root	Dental caries involving the root	Dental caries resulting in pulpitis or periapical abscess or resulting in tooth loss	-	-		
Definition: A disorder characte	rized by the decay of a tooth, in whice	h it becomes softened, discolored	and/or porous.				
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characte	rized by frequent and watery bowel n	novements.					
Dry mouth	Symptomatic (e.g., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva <0.1 ml/min		-		

Duckensil fishula Asymptomistic circinical or disprosition observations only; intervention not indicated intervention in indicated intervention in indicated intervention in indicated intervention in indicated intervention indicated operative intervention indicated urgent intervention indicated ur			Gastrointestinal dis	sorders		
Dudernal fishula Apprendensic, claims or dispersable coherendations only, intervention indicated adaptores coherendations only, intervention indicated adaptores coherendations only, intervention indicated adaptores coherendations only, intervention indicated and intervention indicated and properties the coherendation of the dudernal name and another organ or anatomic site. Dudernal himmorrhage Midic intervention mot indicated with white the dudernal name and another organ or anatomic site. Dudernal characterized by bleeding from the dudernal name of the dudernal name				Grade		
diagnostic observations only, intervention not indicated whether the content of t	Adverse Event	1	2	3	4	5
Declarial hemorrhage Mild; intervention not indicated intervention mild intervention or mild intervention or mild intervention indicated operative intervention indi	Ouodenal fistula	diagnostic observations only;		tube feeding, TPN or hospitalization indicated; elective operative intervention		Death
Intervention or minor cauterization indicated operative intervention indicated operative intervention indicated operative intervention indicated diagnostic observations only, intervention only indicated operative intervention indicated of diagnostic observations only, intervention only indicated operative intervention indicated	Definition: A disorder characte	rized by an abnormal communication	between the duodenum and and	other organ or anatomic site.		
Dudenal obstruction Asymptomatic, clinical or diagnosis observations only; intervention indicated. Definition: A disorder characterized by blockage of the normal flow of stomach contents through the duodenum. Dudenal perforation - Symptomatic, intervention indicated indicated indicated indicated indicated intervention indicated in	Ç		intervention or minor cauterization indicated	endoscopic, or elective		Death
diagnostic observations only; intervention indicated intervention indicated place of the normal flow of stomach contents through the duodenum. Duodenal perforation - Symptomatic; medical intervention indicated wast. Duodenal stenosis Asymptomatic; clinical or diagnostic observations only; intervention indicated wast. Duodenal stenosis Asymptomatic; clinical or diagnostic observations only; intervention indicated wast. Duodenal stenosis Asymptomatic; clinical or diagnostic observations only; intervention indicated, elective operative intervention indicated intervention indicated. Definition: A disorder characterized by a narrowing of the lumen of the duodenum. Duodenal ulcar Asymptomatic; clinical or diagnostic observations only; intervention not indicated, intervention indicated, limiting intervention indicated, limiting intervention indicated, limiting intervention indicated, limiting intervention indicated intervention indicated intervention indicated. Definition: A disorder characterized by a circumscribed, inflammatory and neorotic enosive lesion on the muoscal surface of the duodenal wall. Definition: A disorder characterized by a circumscribed, inflammatory and neorotic enosive lesion on the muoscal surface of the duodenal wall. Definition: A disorder characterized by an uncomfortable, often painful feeling in the stomach, resulting from imparted digestion. Symptoms include burning stomach, bloating, neerburning and altervention indicated intervention indicated intervention indicated intervention indicated intervention indicated intervention indicated wasting synallowing; tube feeding upon the pain intervention indicated wasting synallowing; tube feeding upon the pain intervention indicated wasting synallowing; tube feeding upon the pain intervention indicated wasting synallowing; tube feeding upon the pain intervention indicated wasting synallowing; tube feeding upon the pain intervention indicated wasting synallowing; tube feeding intervention indicated wasting synallowing; tube feeding th	Definition: A disorder characte	rized by bleeding from the duodenur			1	1
Duddenal perforation Symptomatic; medical intervention indicated Severe symptoms; elective operative intervention indicated Life-threatening consequences; ungert operative intervention indicated intervention indicated; limiting intervention indicated ungert operative intervention indicated ungert interv	Duodenal obstruction	diagnostic observations only;		operative intervention indicated;	urgent operative intervention	Death
Definition: A disorder characterized by a rupture in the duodenal wall. Duodenal stenosis Asymptomatic: dinical or disgnostic observations only; intervention indicated with intervention indicated intervention indicated intervention indicated intervention indicated with reading consequences; urgent operative intervention indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disability or endoscopic intervention indicated; limiting self care ADL; disability or endoscopic intervention indicated with reading intervention indicated intervention	Definition: A disorder characte	rized by blockage of the normal flow	of stomach contents through the	duodenum.		
Duddenal stenosis Asymptomatic; clinical or diagnostic observations only; intervention not indicated Definition: A disorder characterized by a narrowing of the lumen of the duodenum. Duddenal ulcer Asymptomatic; clinical or diagnostic observations only; intervention indicated Moderate symptoms; medical intervention indicated. elective operative intervention indicated. elective operative intervention indicated. elective operative intervention indicated. elective operative or endoscopic intervention indicated Definition: A disorder characterized by difficulty in swallowing. Entercoclitis Asymptomatic; clinical or diagnostic observations only; intervention not indicated Definition: A disorder characterized by inflammation of the small and large interstines. Entercovesical fistula Asymptomatic; clinical or diagnostic observations only; intervention not indicated Definition: A disorder characterized by an abnormal communication between the urinary bladder and	Duodenal perforation	-	* *		urgent operative intervention	Death
diagnostic observations only; intervention not indicated Definition: A disorder characterized by a narrowing of the lumen of the duodenum. Duodenal ulcer Asymptomatic; clinical or diagnostic observations only; intervention not indicated Asymptomatic; clinical or diagnostic observations only; intervention indicated Mild symptoms; intervention indicated intervention indicated; limiting self-care ADL; disabiling Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the duodenum indicated intervention indicated; limiting self-care ADL; disabiling Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the duodenum wall. Definition: A disorder characterized by a uncomfortable, often painful feeling in the stomach, resulting from impaired digestion. Symptoms include burning stomach, bloating, nausea and vomiting. Dysphagia Symptomatic, able to eat regular diet regular diet Asymptomatic, clinical or diagnostic observations only; intervention not indicated Asymptomatic; clinical or diagnostic observations only; intervention not indicated Asymptomatic; clinical or diagnostic observations only; intervention not indicated Definition: A disorder characterized by inflammation of the small and large intestines. Enterovesical fistula Asymptomatic; clinical or diagnostic observations only; intervention not indicated Definition: A disorder characterized by inflammation of the small and large intestines. Severe, medically significant; medical intervention indicated Definition: A disorder characterized by an abnormal communication between the urinary bladder and the intestine. Esophageal fistula Asymptomatic; clinical or diagnostic observations only; intervention not indicated Definition: A disorder characterized by an abnormal communication between the esophagus and another organ or anatomic site. Esophageal hemorrhage Mild; intervention indicated Midd; intervention in	Definition: A disorder characte	rized by a rupture in the duodenal w	all.	_	1	,
Dudenal ulcer Asymptomatic; clinical or diagnostic observations only; intervention indicated; limiting instrumental ADL Intervention indicated; limiting set foare ADL; disabling set foare ADL	Duodenal stenosis	diagnostic observations only;		tube feeding; hospitalization indicated; elective operative	urgent operative intervention	Death
diagnostic observations only; intervention indicated; limiting self care ADL; disabiling Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the duodental wall. Despetial Mild symptoms; intervention not indicated intervention indicated; limiting self care ADL; disabiling Definition: A disorder characterized by an uncomfortable, often painful feeling in the stomach, resulting from impaired digestion. Symptoms include burning stomach, bloating, or TPN or hospitalization indicated alting/swallowing and the regular diet symptoms; making and womiting. Definition: A disorder characterized by difficulty in swallowing. Enterocolitis Asymptomatic; clinical or diagnostic observations only; intervention or indicated instervention indicated alting/swallowing and instervention indicated or his part of the part of the part of the duodental wall. Severe symptoms; surgical intervention indicated intervention indicated intervention indicated and womiting. Symptomatic, able to eat regular diet Symptomatic and altered eating/swallowing and altered eating/swallowing urgent intervention indicated or diagnostic observations only; intervention or indicated insteol insteol Definition: A disorder characterized by inflammation of the small and large intestines. Enterovesical fistula Asymptomatic; clinical or diagnostic observations only; intervention indicated intervention indicated intervention indicated or diagnostic observations only; intervention indicated	Definition: A disorder characte	rized by a narrowing of the lumen of	the duodenum.			
Definition: A disorder characterized by difficulty in swallowing. Definition: A disorder characterized by difficulty in swallowing diagnostic observations only; intervention not indicated Definition: A disorder characterized by difficulty in swallowing. Enterocolitis Asymptomatic; clinical or diagnostic observations only; intervention not indicated Definition: A disorder characterized by inflammation of the small and large intestines. Enterovesical fistula Asymptomatic; clinical or diagnostic observations only; intervention not indicated Definition: A disorder characterized by an abnormal communication between the urinary bladder and the intestine. Esophageal fistula Definition: A disorder characterized by an abnormal communication between the esophagus and another organ or anatomic site. Esophageal hemorrhage Mild; intervention not indicated Moderate symptoms; surgicin intervention indicated intervention indicated intervention indicated. Severely altered gl function; tube feeding, provided intervention indicated intervention indicated intervention indicated. Severely altered Gl function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated intervention indicated. Definition: A disorder characterized by an abnormal communication between the esophagus and another organ or anatomic site. Esophageal hemorrhage Mild; intervention not indicated Moderate symptoms; medical intervention indicated intervention indicated. Moderate symptoms; surgitical tered gl gating from impaired digestion. Symptomatic; nonivasive intervention indicated in the provided provided in the p	Ouodenal ulcer	diagnostic observations only;	intervention indicated; limiting	TPN indicated; elective operative or endoscopic intervention indicated; limiting	urgent operative intervention	Death
indicated intervention	Definition: A disorder characte	rized by a circumscribed, inflammato	ory and necrotic erosive lesion on	the mucosal surface of the duoder	nal wall.	
Dysphagia Symptomatic, able to eat regular diet Symptomatic and altered eating/swallowing Severely altered eating/swallowing; tube feeding or TPN or hospitalization indicated Severe or persistent abdominal pain; fever; ileus; peritoneal signs Definition: A disorder characterized by inflammation of the small and large intestines. Enterovesical fistula Asymptomatic; clinical or diagnostic observations only; intervention not indicated intervention not indicated by an abnormal communication between the urinary bladder and the intestine. Esophageal fistula Asymptomatic; clinical or diagnostic observations only; intervention not indicated by an abnormal communication between the esophagus and another organ or anatomic site. Esophageal hemorrhage Mild; intervention not indicated Moderate symptoms; medical Transfusion, radiologic, Life-threatening consequences; urgent intervention indicated between the esophagus and another organ or anatomic site. Esophageal hemorrhage Mild; intervention not indicated Moderate symptoms; medical Transfusion, radiologic, Life-threatening consequences; beating acting act	Dyspepsia				-	-
Symptomatic, able to eat regular diet Symptomatic, able to eat regular diet Symptomatic and altered eating/swallowing surgent intervention indicated Definition: A disorder characterized by difficulty in swallowing. Enterocolitis Asymptomatic; clinical or diagnostic observations only; intervention not indicated Asymptomatic; clinical or diagnostic observations only; intervention not indicated Asymptomatic; clinical or diagnostic observations only; intervention not indicated Definition: A disorder characterized by inflammation of the small and large intestines. Enterovesical fistula Asymptomatic; clinical or diagnostic observations only; intervention not indicated Definition: A disorder characterized by an abnormal communication between the urinary bladder and the intestine. Esophageal fistula Asymptomatic; clinical or diagnostic observations only; intervention not indicated Definition: A disorder characterized by an abnormal communication between the urinary bladder and the intestine. Esophageal fistula Definition: A disorder characterized by an abnormal communication between the esophagus and another organ or anatomic site. Esophageal hemorrhage Mild; intervention not indicated Moderate symptoms; medical Transfusion, radiologic, Life-threatening consequences; urgent intervention indicated Life-threatening consequences; u			nful feeling in the stomach, resulti	ing from impaired digestion. Sympt	oms include burning stomach, blo	ating,
Enterocolitis Asymptomatic; clinical or diagnostic observations only; intervention not indicated Definition: A disorder characterized by inflammation of the small and large intestines. Enterovesical fistula Asymptomatic; clinical or diagnostic observations only; intervention not indicated Asymptomatic; clinical or diagnostic observations only; intervention not indicated Definition: A disorder characterized by an abnormal communication between the urinary bladder and the intestine. Esophageal fistula Asymptomatic; clinical or diagnostic observations only; intervention not indicated Definition: A disorder characterized by an abnormal communication between the urinary bladder and the intestine. Esophageal fistula Asymptomatic; clinical or diagnostic observations only; intervention not indicated Definition: A disorder characterized by an abnormal communication between the esophagus and another organ or anatomic site. Esophageal hemorrhage Mild; intervention not indicated Moderate symptoms; medical Severe or persistent abdominal pain; fever; ileus; peritoneal signs Severe, medically significant; medically significant; medical signs Life-threatening consequences; urgent intervention indicated Definition: A disorder characterized by an abnormal communication between the esophagus and another organ or anatomic site. Esophageal hemorrhage Mild; intervention not indicated Moderate symptoms; medical Transfusion, radiologic, Life-threatening consequences; paths and path		Symptomatic, able to eat		eating/swallowing; tube feeding or TPN or hospitalization	- '	Death
diagnostic observations only; intervention not indicated Definition: A disorder characterized by inflammation of the small and large intestines. Enterovesical fistula Asymptomatic; clinical or diagnostic observations only; intervention not indicated Definition: A disorder characterized by an abnormal communication between the urinary bladder and the intestine. Esophageal fistula Asymptomatic; clinical or diagnostic observations only; intervention indicated Asymptomatic; clinical or diagnostic observations only; intervention indicated Asymptomatic; clinical or diagnostic observations only; intervention not indicated Definition: A disorder characterized by an abnormal communication between the urinary bladder and the intestine. Esophageal fistula Asymptomatic; clinical or diagnostic observations only; intervention not indicated Bymptomatic; altered GI Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated elective operative intervention indicated Definition: A disorder characterized by an abnormal communication between the esophagus and another organ or anatomic site. Esophageal hemorrhage Mild; intervention not indicated Moderate symptoms; medical Transfusion, radiologic, Life-threatening consequences; Death	Definition: A disorder characte	rized by difficulty in swallowing.	,			•
Enterovesical fistula Asymptomatic; clinical or diagnostic observations only; intervention indicated Definition: A disorder characterized by an abnormal communication between the urinary bladder and the intestine. Esophageal fistula Asymptomatic; clinical or diagnostic observations only; intervention indicated Asymptomatic; clinical or diagnostic observations only; intervention not indicated Definition: A disorder characterized by an abnormal communication between the urinary bladder and the intestine. Symptomatic; altered GI severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated elective operative intervention indicated. Definition: A disorder characterized by an abnormal communication between the esophagus and another organ or anatomic site. Esophageal hemorrhage Mild; intervention not indicated Moderate symptoms; medical Transfusion, radiologic, Life-threatening consequences; urgent intervention indicated Life-threatening consequences; Death	Enterocolitis	diagnostic observations only;	· ·	pain; fever; ileus; peritoneal		Death
diagnostic observations only; intervention indicated Definition: A disorder characterized by an abnormal communication between the urinary bladder and the intestine. Esophageal fistula Asymptomatic; clinical or diagnostic observations only; intervention not indicated Symptomatic; altered GI function Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated; elective operative intervention indicated Definition: A disorder characterized by an abnormal communication between the esophagus and another organ or anatomic site. Esophageal hemorrhage Mild; intervention not indicated Moderate symptoms; medical Transfusion, radiologic, Life-threatening consequences; Death	Definition: A disorder characte	rized by inflammation of the small ar	nd large intestines.		T	
Asymptomatic; clinical or diagnostic observations only; intervention not indicated Asymptomatic; clinical or diagnostic observations only; intervention not indicated Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated; elective operative intervention indicated Definition: A disorder characterized by an abnormal communication between the esophagus and another organ or anatomic site. Esophageal hemorrhage Mild; intervention not indicated Moderate symptoms; medical Transfusion, radiologic, Life-threatening consequences; Death	Enterovesical fistula	diagnostic observations only;				Death
diagnostic observations only; intervention not indicated function tube feeding, TPN or hospitalization indicated; elective operative intervention indicated; elective operative intervention indicated Definition: A disorder characterized by an abnormal communication between the esophagus and another organ or anatomic site. Esophageal hemorrhage Mild; intervention not indicated Moderate symptoms; medical Transfusion, radiologic, Life-threatening consequences; Death	Definition: A disorder characte	rized by an abnormal communication	between the urinary bladder and	d the intestine.		
Esophageal hemorrhage Mild; intervention not indicated Moderate symptoms; medical Transfusion, radiologic, Life-threatening consequences; Death	Esophageal fistula	diagnostic observations only;		tube feeding, TPN or hospitalization indicated; elective operative intervention		Death
	Definition: A disorder characte	rized by an abnormal communication	n between the esophagus and an	other organ or anatomic site.		
cauterization indicated operative intervention indicated	Esophageal hemorrhage	Mild; intervention not indicated	intervention or minor	endoscopic, or elective		Death

Gastrointestinal disorders							
Grade							
Adverse Event	1	2	3	4	5		
Esophageal necrosis	-	-	Inability to aliment adequately by GI tract; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder characte	erized by a necrotic process occurring	g in the esophageal wall.					
Esophageal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characte	erized by blockage of the normal flow	of the contents in the esophagus	T	T			
Esophageal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-		
Definition: A disorder characte	rized by a sensation of marked disco	omfort in the esophageal region.					
Esophageal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
	erized by a rupture in the wall of the e	1	1	<u> </u>			
Esophageal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder characte	rized by a narrowing of the lumen of	the esophagus.					
Esophageal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder characte	erized by a circumscribed, inflammate	ory and necrotic erosive lesion on	the mucosal surface of the esopha	geal wall.			
Esophageal varices hemorrhage	-	Self-limited; intervention not indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characte	rized by bleeding from esophageal v	varices.					
Esophagitis Definition: A disorder characte	Asymptomatic; clinical or diagnostic observations only; intervention not indicated erized by inflammation of the esophar	Symptomatic; altered eating/swallowing; oral supplements indicated	Severely altered eating/swallowing; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Fecal incontinence	Occasional use of pads required		Severe symptoms; elective operative intervention indicated	-	-		
Definition: A disorder characte	rized by inability to control the escap	be of stool from the rectum.	•	•	•		
Flatulence	Mild symptoms; intervention not indicated	psychosocial sequelae	-	-	-		
	erized by a state of excessive gas in		0		D41-		
Gastric fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; bowel rest; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder characte	erized by an abnormal communication	n between the stomach and anoth	ner organ or anatomic site.	T			
Gastric hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characte	erized by bleeding from the gastric wa	all.	1	ı			
Gastric necrosis	-	-	Inability to aliment adequately by GI tract; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
	t .	1	1	1			

Gastrointestinal disorders								
Grade								
Adverse Event	1	2	3	4	5			
Gastric perforation Definition: A disorder character	- rized by a rupture in the stomach wa	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
			Soverely altered Cl function:	Life threatening consequences:	Death			
Gastric stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Deam			
Definition: A disorder character	rized by a narrowing of the lumen of	the stomach.	_					
Gastric ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death			
	rized by a circumscribed, inflammato	ory and necrotic erosive lesion on						
Gastritis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated	Severely altered eating or gastric function; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder character	rized by inflammation of the stomach	1. T	T	T				
Gastroesophageal reflux disease	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; surgical intervention indicated	-	-			
	rized by reflux of the gastric and/or d y result in injury to the esophageal m			nd usually caused by incompetend	e of the lov			
Gastrointestinal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder character	rized by an abnormal communication	between any part of the gastroin	testinal system and another organ	or anatomic site.				
Gastrointestinal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder character	rized by a sensation of marked disco	omfort in the gastrointestinal region	٦.					
Gastroparesis	Mild nausea, early satiety and bloating, able to maintain caloric intake on regular diet	Moderate symptoms; able to maintain nutrition with dietary and lifestyle modifications; may need pharmacologic intervention	Weight loss; refractory to medical intervention; unable to maintain nutrition orally		-			
Definition: A disorder character	rized by an incomplete paralysis of th	he muscles of the stomach wall re	sulting in delayed emptying of the	gastric contents into the small inte	estine.			
Gingival pain	Mild pain	Moderate pain interfering with oral intake	Severe pain; inability to aliment orally	-	-			
Definition: A disorder character	rized by a sensation of marked disco	omfort in the gingival region.	T	T				
Hemorrhoidal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder character	rized by bleeding from the hemorrho	ids.	T	T				
Hemorrhoids	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; banding or medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	-	-			
Definition: A disorder character	rized by the presence of dilated veins	s in the rectum and surrounding a	rea.					
leal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder character	rized by an abnormal communication	between the ileum and another of	organ or anatomic site.					
lleal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
	•	•	•	•				

		Gastrointestinal dis			
			Grade		
Adverse Event	1	2	3	4	5
leal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteria	zed by blockage of the normal flow	of the intestinal contents in the ile	eum.	i	
leal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteri	zed by a rupture in the ileal wall.			T	
leal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered Gl function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteri:	zed by a narrowing of the lumen of	the ileum.		T	1
lleal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterize	zed by a circumscribed, inflammato	ory and necrotic erosive lesion on	the mucosal surface of the ileum.	Γ	
leus	- zed by failure of the ileum to transp	Symptomatic; altered GI function; bowel rest indicated	Severely altered GI function; TPN indicated	Life-threatening consequences; urgent intervention indicated	Death
Intra-abdominal hemorrhage	led by failure of the flediff to trainsp	Medical intervention or minor	Transfusion, radiologic,	Life-threatening consequences;	Death
nii a-abuoniinai nemormage		cauterization indicated	endoscopic, or elective operative intervention indicated	urgent intervention indicated	Death
Definition: A disorder characteri:	zed by bleeding in the abdominal c	avity.			
Jejunal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteri:	' zed by an abnormal communication	n between the jejunum and anoth	er organ or anatomic site.		•
Jejunal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteri:	zed by bleeding from the jejunal wa	all.	,	!	
Jejunal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteri:	zed by blockage of the normal flow	of the intestinal contents in the je	ejunum.		
Jejunal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteri.	ा zed by a rupture in the jejunal wall.	•	•	•	•
Jejunal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteri:	zed by a narrowing of the lumen of	the jejunum.			
Jejunal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteri.	zed by a circumscribed, inflammato	ory and necrotic erosive lesion on	the mucosal surface of the jejunun	1.	
ip pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-

		Gastrointestinal dis	orders			
			Grade			
Adverse Event	1	2	3	4	5	
Lower gastrointestinal	Mild; intervention not indicated	Moderate symptoms; medical	Transfusion, radiologic,	Life-threatening consequences;	Death	
hemorrhage		intervention or minor	endoscopic, or elective	urgent intervention indicated		
		cauterization indicated	operative intervention indicated			
Definition: A disorder characte	erized by bleeding from the lower gas	strointestinal tract (small intestine,	large intestine, and anus).	T	1	
Malabsorption	-	Altered diet; oral intervention indicated	Inability to aliment adequately; TPN indicated	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characte	erized by inadequate absorption of nu	utrients in the small intestine. Sym	ptoms include abdominal marked	discomfort, bloating and diarrhea.		
Mucositis oral	Asymptomatic or mild	Moderate pain; not interfering	Severe pain; interfering with oral	Life-threatening consequences;	Death	
	symptoms; intervention not	with oral intake; modified diet	intake	urgent intervention indicated		
	indicated	indicated				
Definition: A disorder characte	erized by inflammation of the oral mu	cosal.		1	1	
Nausea	Loss of appetite without	Oral intake decreased without	Inadequate oral caloric or fluid	-	-	
	alteration in eating habits	significant weight loss,	intake; tube feeding, TPN, or			
		dehydration or malnutrition	hospitalization indicated			
	erized by a queasy sensation and/or					
Obstruction gastric	Asymptomatic; clinical or	Symptomatic; altered Gl	Hospitalization indicated;	Life-threatening consequences;	Death	
	diagnostic observations only; intervention not indicated	function; limiting instrumental ADL	elective operative intervention	urgent operative intervention indicated		
	antervention not indicated	,,,,,,,	indicated; limiting self care ADL; disabling	maioatou		
Definition: A disorder characte	। erized by blockage of the normal flow	of the contents in the stomach	-	I	ı	
Oral cavity fistula	Asymptomatic; clinical or	Symptomatic; altered GI	Severely altered GI function;	Life-threatening consequences;	Death	
Oral Cavity listula	diagnostic observations only;	function	TPN or hospitalization indicated;	urgent intervention indicated	Dealii	
	intervention not indicated	Tanonom	elective operative intervention	argone intorvention indicated		
			indicated			
Definition: A disorder characte	erized by an abnormal communication	n between the oral cavity and ano	ther organ or anatomic site.			
Oral dysesthesia	Mild discomfort; not interfering	Moderate pain; interfering with	Disabling pain; tube feeding or	-	-	
,	with oral intake	oral intake	TPN indicated			
Definition: A disorder characte	erized by a burning or tingling sensat	ion on the lips, tongue or entire m	outh.			
Oral hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical	Transfusion, radiologic,	Life-threatening consequences;	Death	
•		intervention or minor	endoscopic, or elective	urgent intervention indicated		
		cauterization indicated	operative intervention indicated			
Definition: A disorder characte	erized by bleeding from the mouth.					
Oral pain	Mild pain	Moderate pain; limiting	Severe pain; limiting self care	-	-	
		instrumental ADL	ADL			
Definition: A disorder characte	erized by a sensation of marked disco	omfort in the mouth, tongue or lips	.			
Pancreatic duct stenosis	Asymptomatic; clinical or	Symptomatic; altered GI	Severely altered GI function;	Life-threatening consequences;	Death	
	diagnostic observations only;	function	tube feeding or hospitalization	urgent operative intervention		
	intervention not indicated		indicated; elective operative	indicated		
		1	intervention indicated	I	1	
Definition: A disorder characte	erized by a narrowing of the lumen of			Τ	1	
Pancreatic fistula	Asymptomatic; clinical or	Symptomatic; altered GI	Severely altered GI function;	Life-threatening consequences;	Death	
	diagnostic observations only;	function	tube feeding or TPN or	urgent operative intervention		
	intervention not indicated		hospitalization indicated;	indicated		
			elective operative intervention indicated			
Definition: A disorder characte	 erized by an abnormal communication	I n hetween the nancreas and cost	1	I	1	
	I an abhornal communication	· ·	1	l ifa threataning	Da-45	
	Milduinton continue - + in -li-	Moderate symptoms; medical	Transfusion, radiologic, endoscopic, or elective	Life-threatening consequences; urgent intervention indicated	Death	
	Mild; intervention not indicated	intervention or minor		argorit intervention indicated		
	Mild; intervention not indicated	intervention or minor cauterization indicated				
Pancreatic hemorrhage		cauterization indicated	operative intervention indicated		1	
Pancreatic hemorrhage Definition: A disorder characte	Mild; intervention not indicated erized by bleeding from the pancreas	cauterization indicated	operative intervention indicated	l ife threatening	Do-#	
Pancreatic hemorrhage		cauterization indicated	operative intervention indicated Tube feeding or TPN indicated;	Life-threatening consequences;	Death	
Pancreatic hemorrhage Definition: A disorder characte		cauterization indicated	Tube feeding or TPN indicated; radiologic, endoscopic, or	urgent operative intervention	Death	
Pancreatic hemorrhage Definition: A disorder characte Pancreatic necrosis	erized by bleeding from the pancreas	cauterization indicated	operative intervention indicated Tube feeding or TPN indicated;	- '	Death	
Pancreatic hemorrhage Definition: A disorder characte Pancreatic necrosis Definition: A disorder characte		cauterization indicated - g in the pancreas.	Tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	urgent operative intervention indicated		
Pancreatic hemorrhage Definition: A disorder characte Pancreatic necrosis	erized by bleeding from the pancreas	cauterization indicated	Tube feeding or TPN indicated; radiologic, endoscopic, or	urgent operative intervention	Death	

Gastrointestinal disorders							
			Grade				
Adverse Event	1	2	3	4	5		
Definition: A disorder characteriz	zed by inflammation of the pancrea	S.	ı				
Periodontal disease	Gingival recession or gingivitis; limited bleeding on probing; mild local bone loss	Moderate gingival recession or gingivitis; multiple sites of bleeding on probing; moderate bone loss	Spontaneous bleeding; severe bone loss with or without tooth loss; osteonecrosis of maxilla or mandible	-	-		
Definition: A disorder in the ging	ival tissue around the teeth.		1				
Peritoneal necrosis	-	-	Tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder characterize	zed by a necrotic process occurring	in the peritoneum.	1	T			
Proctitis	Rectal discomfort, intervention not indicated	Symptoms (e.g., rectal discomfort, passing blood or mucus); medical intervention indicated; limiting instrumental ADL	Severe symptoms; fecal urgency or stool incontinence; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteriz	zed by inflammation of the rectum.						
Rectal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteriz	zed by an abnormal communication	n between the rectum and another	organ or anatomic site.				
Rectal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteriz	zed by bleeding from the rectal wal	and discharged from the anus.					
Rectal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder characterize	zed by inflammation of the mucous	membrane of the rectum.	1	<u> </u>			
Rectal necrosis	-	-	Tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder characteriz	zed by a necrotic process occurring	in the rectal wall.					
Rectal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder characteriz	zed by blockage of the normal flow	of the intestinal contents in the re	ctum.	Ī			
Rectal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-		
Definition: A disorder characterize	zed by a sensation of marked disco	omfort in the rectal region.	1	T			
Rectal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder characterize	zed by a rupture in the rectal wall.	T	1	T			
Rectal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder characteriz	zed by a narrowing of the lumen of	the rectum.					
Rectal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function (e.g. altered dietary habits, vomiting, diarrhea)	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death		

Grade							
Adverse Event	1	2	Grade 3	4	5		
Adverse Event	1			4			
Retroperitoneal hemorrhage	-	Self-limited; intervention indicated	Transfusion, medical, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteri:	zed by bleeding from the retroperite	oneal area.	T		1		
Salivary duct inflammation	Slightly thickened saliva; slightly altered taste (e.g., metallic)	Thick, ropy, sticky saliva; markedly altered taste; alteration in diet indicated; secretion-induced symptoms; limiting instrumental ADL	Acute salivary gland necrosis; severe secretion-induced symptoms (e.g., thick saliva/oral secretions or gagging); tube feeding or TPN indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteri:	zed by inflammation of the salivary	duct.					
Salivary gland fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; tube feeding indicated	Severely altered GI function; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder characteri:	zed by an abnormal communication	between a salivary gland and an	other organ or anatomic site.				
Small intestinal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe pain; interfering with oral intake; tube feeding, TPN or hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteri:	zed by inflammation of the mucous	membrane of the small intestine.					
Small intestinal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder characteriz	zed by blockage of the normal flow	of the intestinal contents.					
Small intestinal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder characteri:	zed by a rupture in the small intesti	ne wall.					
Small intestinal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Symptomatic and severely altered GI function; tube feeding, TPN or hospitalization indicated; non-emergent operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder characteriz	zed by a narrowing of the lumen of	the small intestine.					
Small intestine ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder characteri:	zed by a circumscribed, inflammato	ory and necrotic erosive lesion on	the mucosal surface of the small in	itestine.			
Stomach pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-		
Definition: A disorder characteri:	zed by a sensation of marked disco	omfort in the stomach.	1	I			
Tooth development disorder	Asymptomatic; hypoplasia of tooth or enamel	Impairment correctable with oral surgery	Maldevelopment with impairment not surgically correctable; disabling	-	-		
Definition: A disorder characterize	zed by a pathological process of th	e teeth occurring during tooth dev	elopment.	Γ			
Tooth discoloration	Surface stains	-	-	-	-		
Definition: A disorder characterize	zed by a change in tooth hue or tin	t.	1	1			
oothache	Mild pain	Moderate pain; limiting	Severe pain; limiting self care	-	-		

Gastrointestinal disorders								
	Grade							
Adverse Event	1	2	3	4	5			
Typhlitis	-	-	Symptomatic (e.g., abdominal pain, fever, change in bowel habits with ileus); peritoneal signs	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characteriz	ed by inflammation of the cecum.							
Upper gastrointestinal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteriz	ed by bleeding from the upper gas	trointestinal tract (oral cavity, pha	rynx, esophagus, and stomach).					
Vomiting	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	>=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteriz	ed by the reflexive act of ejecting t	he contents of the stomach throug	gh the mouth.	•				
Gastrointestinal disorders - Other, specify	, , ,	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death			

			Grade		
Adverse Event	1	2	3	4	5
Chills	Mild sensation of cold;	Moderate tremor of the entire	Severe or prolonged, not	-	-
Definition: A disorder charac	shivering; chattering of teeth sterized by a sensation of cold that ofte	body; narcotics indicated	responsive to narcotics		l
Death neonatal	serized by a serisation of cold that one	marks a physiologic response to	sweating after a rever.		Death
	terized by cessation of life occurring d	l - uring the first 28 days of life.	1-	1-	Dealli
Death NOS	-	-	-	-	Death
Definition: A cessation of life	that cannot be attributed to a CTCAE	term associated with Grade 5.			
Edema face	Localized facial edema	Moderate localized facial edema; limiting instrumental ADL	Severe swelling; limiting self care ADL	-	-
Definition: A disorder charac	cterized by swelling due to excessive flo	uid accumulation in facial tissues.			
Edema limbs	5 - 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection	>10 - 30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL	>30% inter-limb discrepancy in volume; gross deviation from normal anatomic contour; limiting self care ADL	-	-
Definition: A disorder charac	terized by swelling due to excessive flu	uid accumulation in the upper or lo	wer extremities.		
Edema trunk	Swelling or obscuration of anatomic architecture on close inspection	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL	Gross deviation from normal anatomic contour; limiting self care ADL	-	-
Facial pain	terized by swelling due to excessive fli Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care	-	-
Deficition A discorder descri		1	INDL	ļ	ı
	eterized by a sensation of marked disco				
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL	-	-
Definition: A disorder charac	cterized by a state of generalized weak	ness with a pronounced inability to	summon sufficient energy to acc	omplish daily activities.	
Fever	38.0 - 39.0 degrees C (100.4 - 102.2 degrees F)	>39.0 - 40.0 degrees C (102.3 - 104.0 degrees F)	>40.0 degrees C (>104.0 degrees F) for <=24 hrs	>40.0 degrees C (>104.0 degrees F) for >24 hrs	Death
Definition: A disorder charac	terized by elevation of the body's temp	erature above the upper limit of n	ormal.	'	•
Flu like symptoms	Mild flu-like symptoms present	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder charac	l cterized by a group of symptoms simila	1	1	I ody aches, malaise, loss of appet	ite and dry
Gait disturbance	Mild change in gait (e.g., wide-	Moderate change in gait (e.g.,	Disabling; limiting self care ADL	_	
	based, limping or hobbling)	wide-based, limping or hobbling); assistive device indicated; limiting instrumental ADL	Disability, lithling sell care ADL		-
Definition: A disorder charac	terized by walking difficulties.	I	Ι	1	1
Hypothermia	-	35 - >32 degrees C; 95 - >89.6 degrees F	32 - >28 degrees C; 89.6 - >82.4 degrees F	<=28 degrees C; 82.4 degrees F; life-threatening consequences (e.g., coma, hypotension, pulmonary edema, acidemia, ventricular fibrillation)	1

		disorders and administra	Grade		
Adverse Event	1	2	3	4	5
nfusion related reaction	Mild transient reaction; infusion	Therapy or infusion interruption	Prolonged (e.g., not rapidly	Life-threatening consequences;	Death
illiusion relateu reaction	interruption not indicated;	indicated but responds promptly	responsive to symptomatic	urgent intervention indicated	Death
	intervention not indicated	to symptomatic treatment (e.g.,	medication and/or brief	argoni intervention indicated	
	intervention net maietate	antihistamines, NSAIDS,	interruption of infusion);		
		narcotics, IV fluids); prophylactic			
		medications indicated for <=24	following initial improvement;		
		hrs	hospitalization indicated for		
			clinical sequelae		
Definition: A disorder characteriz	। zed by adverse reaction to the infus	ı sion of pharmacological or biologic		I	1
nfusion site extravasation	,	Erythema with associated	Ulceration or necrosis; severe	Life-threatening consequences;	Death
The same that are same to the		symptoms (e.g., edema, pain,	tissue damage; operative	urgent intervention indicated	Dou
		induration, phlebitis)	intervention indicated	angent intervention introduce	
Definition: A disorder characteria	। zed by leakage of a pharmacologic	, , , ,	1	I sella. Signs and symptoms include	l e induratio
	sation and marked discomfort at the	•	musion site into the surrounding to	sauc. Oigna and symptoma moldus	o induratio
njection site reaction	Tenderness with or without	Pain; lipodystrophy; edema;	Ulceration or necrosis; severe	Life-threatening consequences;	Death
•	associated symptoms (e.g.,	phlebitis	tissue damage; operative	urgent intervention indicated	
	warmth, erythema, itching)	•	intervention indicated		
Definition: A disorder characteriz	zed by an intense adverse reaction	ı (usually immunologic) developing	1	I	1
rritability	Mild; easily consolable	Moderate; limiting instrumental	Severe abnormal or excessive	_	_
masiny	Wind, Cabily Corrobiable	ADL; increased attention	response; limiting self care ADL;		
		indicated	inconsolable		
5 5 W A II A II A I		ļ	1	l	1
Definition: A disorder characterize	zed by an abnormal responsivenes	s to stimuli or physiological arousa	ar; may be in response to pain, ing	nt, a drug, an emotional situation (or a medic
_ocalized edema	Localized to dependent areas,	Moderate localized edema and	Severe localized edema and	-	_
	no disability or functional	intervention indicated; limiting	intervention indicated; limiting		
	impairment	instrumental ADL	self care ADL		
Definition: Δ disorder characteria	ed by swelling due to excessive flu	ı	1	ı	ı
Malaise	Uneasiness or lack of well being	·	omic sitc.		
vialaise	Office strices of fack of well being	being; limiting instrumental ADL	-	-	-
			1	l	I
Definition: A disorder characteria	red by a feeling of general discomf	art or unesciness an out-of-sorts			
	red by a feeling of general discomfo	ort or uneasiness, an out-of-sorts		Life threatening concessioned	Dooth
	red by a feeling of general discomfe	ort or uneasiness, an out-of-sorts	Shock with azotemia and acid-	Life-threatening consequences	Death
	ted by a feeling of general discomform	ort or uneasiness, an out-of-sorts	Shock with azotemia and acid- base disturbances; significant	(e.g., vasopressor dependent	Death
	ted by a feeling of general discomfo	ort or uneasiness, an out-of-sorts	Shock with azotemia and acid-	(e.g., vasopressor dependent and oliguric or anuric or	Death
	ted by a feeling of general discomfo	ort or uneasiness, an out-of-sorts	Shock with azotemia and acid- base disturbances; significant	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic	Death
Multi-organ failure	-	-	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities	(e.g., vasopressor dependent and oliguric or anuric or	Death
Multi-organ failure Definition: A disorder characteriz	eed by progressive deterioration of	the lungs, liver, kidney and clottin	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic	Death
Multi-organ failure	eed by progressive deterioration of Asymptomatic localized neck	the lungs, liver, kidney and clottin Moderate neck edema; slight	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities g mechanisms.	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic	Death
Multi-organ failure Definition: A disorder characteriz	eed by progressive deterioration of	- the lungs, liver, kidney and clottin Moderate neck edema; slight obliteration of anatomic	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities g mechanisms. Generalized neck edema (e.g., difficulty in turning neck);	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic	Death
Multi-organ failure Definition: A disorder characteriz	eed by progressive deterioration of Asymptomatic localized neck	the lungs, liver, kidney and clottin Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities g mechanisms.	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic	Death
Multi-organ failure Definition: A disorder characteriz Neck edema	eed by progressive deterioration of Asymptomatic localized neck edema	the lungs, liver, kidney and clottin Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities g mechanisms. Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic	Death -
Multi-organ failure Definition: A disorder characteriz Neck edema Definition: A disorder characteriz	ced by progressive deterioration of Asymptomatic localized neck edema	the lungs, liver, kidney and clotting Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL tition of excessive fluid in the neck	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities g mechanisms. Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic	Death -
Multi-organ failure Definition: A disorder characteriz Neck edema Definition: A disorder characteriz	eed by progressive deterioration of Asymptomatic localized neck edema	the lungs, liver, kidney and clotting Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL tition of excessive fluid in the neck	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities g mechanisms. Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL Severe pain; limiting self care	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic	Death -
Multi-organ failure Definition: A disorder characteriz Neck edema Definition: A disorder characteriz Non-cardiac chest pain	ced by progressive deterioration of Asymptomatic localized neck edema ed by swelling due to an accumula	the lungs, liver, kidney and clotting Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL tion of excessive fluid in the neck Moderate pain; limiting instrumental ADL	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities g mechanisms. Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic	Death -
Multi-organ failure Definition: A disorder characteriz Neck edema Definition: A disorder characteriz Non-cardiac chest pain Definition: A disorder characteriz	ced by progressive deterioration of Asymptomatic localized neck edema ted by swelling due to an accumula Mild pain	the lungs, liver, kidney and clotting Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL tition of excessive fluid in the neck Moderate pain; limiting instrumental ADL ated to a heart disorder.	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities g mechanisms. Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL Severe pain; limiting self care ADL	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic	Death -
Multi-organ failure Definition: A disorder characteriz Neck edema Definition: A disorder characteriz Non-cardiac chest pain Definition: A disorder characteriz	ced by progressive deterioration of Asymptomatic localized neck edema ed by swelling due to an accumula	the lungs, liver, kidney and clotting Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL tition of excessive fluid in the neck Moderate pain; limiting instrumental ADL ated to a heart disorder. Moderate pain; limiting	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities g mechanisms. Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL Severe pain; limiting self care ADL	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic	Death -
Multi-organ failure Definition: A disorder characteriz Neck edema Definition: A disorder characteriz Non-cardiac chest pain Definition: A disorder characteriz Pain	eed by progressive deterioration of Asymptomatic localized neck edema ted by swelling due to an accumulated by discomfort in the chest unrelegation.	the lungs, liver, kidney and clottin Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL tion of excessive fluid in the neck Moderate pain; limiting instrumental ADL ated to a heart disorder. Moderate pain; limiting instrumental ADL	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities g mechanisms. Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL Severe pain; limiting self care ADL	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic	Death -
Multi-organ failure Definition: A disorder characteriz Neck edema Definition: A disorder characteriz Non-cardiac chest pain Definition: A disorder characteriz Pain Definition: A disorder characteriz	ced by progressive deterioration of Asymptomatic localized neck edema ted by swelling due to an accumula Mild pain	the lungs, liver, kidney and clottin Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL tion of excessive fluid in the neck Moderate pain; limiting instrumental ADL ated to a heart disorder. Moderate pain; limiting instrumental ADL	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities g mechanisms. Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL Severe pain; limiting self care ADL	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic acidosis)	-
Multi-organ failure Definition: A disorder characteriz Neck edema Definition: A disorder characteriz Non-cardiac chest pain Definition: A disorder characteriz Pain Definition: A disorder characteriz Sudden death NOS	eed by progressive deterioration of Asymptomatic localized neck edema eed by swelling due to an accumulated by discomfort in the chest unreleased by the sensation of marked discomfort in the discomfort in the chest unreleased by the sensation of marked discomfort in the chest unreleased by the sensation of the chest unreleased by the chest unreleased by the chest unrel	the lungs, liver, kidney and clotting Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL tition of excessive fluid in the neck Moderate pain; limiting instrumental ADL ated to a heart disorder. Moderate pain; limiting instrumental ADL comfort, distress or agony.	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities g mechanisms. Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL Severe pain; limiting self care ADL Severe pain; limiting self care	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic	Death Death
Multi-organ failure Definition: A disorder characteriz Neck edema Definition: A disorder characteriz Non-cardiac chest pain Definition: A disorder characteriz Pain Definition: A disorder characteriz Sudden death NOS Definition: An unexpected cessa	eed by progressive deterioration of Asymptomatic localized neck edema eed by swelling due to an accumulated by discomfort in the chest unreleful pain eed by the sensation of marked discussion of life that cannot be attributed	the lungs, liver, kidney and clotting Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL tion of excessive fluid in the neck Moderate pain; limiting instrumental ADL lated to a heart disorder. Moderate pain; limiting instrumental ADL comfort, distress or agony. - to a CTCAE term associated with	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities g mechanisms. Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL Severe pain; limiting self care ADL Severe pain; limiting self care ADL	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic acidosis) -	Death
Multi-organ failure Definition: A disorder characteriz Neck edema Definition: A disorder characteriz Non-cardiac chest pain Definition: A disorder characteriz Pain Definition: A disorder characteriz Sudden death NOS Definition: An unexpected cessa General disorders and	eed by progressive deterioration of Asymptomatic localized neck edema eed by swelling due to an accumula Mild pain eed by discomfort in the chest unrel Mild pain eed by the sensation of marked disc toon of life that cannot be attributed Asymptomatic or mild	the lungs, liver, kidney and clotting Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL stion of excessive fluid in the neck Moderate pain; limiting instrumental ADL ated to a heart disorder. Moderate pain; limiting instrumental ADL comfort, distress or agony. - to a CTCAE term associated with	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities g mechanisms. Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL Severe pain; limiting self care ADL Severe pain; limiting self care ADL - n Grade 5. Severe or medically significant	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic acidosis) - - Life-threatening consequences;	-
Multi-organ failure Definition: A disorder characteriz Neck edema Definition: A disorder characteriz Non-cardiac chest pain Definition: A disorder characteriz Pain Definition: A disorder characteriz Sudden death NOS Definition: An unexpected cessa General disorders and administration site conditions -	ted by progressive deterioration of Asymptomatic localized neck edema and by swelling due to an accumulated by discomfort in the chest unreleading by the sensation of marked discomplete of the complete of	the lungs, liver, kidney and clottine Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL tition of excessive fluid in the neck Moderate pain; limiting instrumental ADL ated to a heart disorder. Moderate pain; limiting instrumental ADL comfort, distress or agony. - to a CTCAE term associated with Moderate; minimal, local or noninvasive intervention	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities g mechanisms. Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL Severe pain; limiting self care ADL Severe pain; limiting self care ADL - a Grade 5. Severe or medically significant but not immediately life-	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic acidosis) -	Death
Multi-organ failure Definition: A disorder characteriz Neck edema Definition: A disorder characteriz Non-cardiac chest pain Definition: A disorder characteriz Pain Definition: A disorder characteriz Sudden death NOS Definition: An unexpected cessa	eed by progressive deterioration of Asymptomatic localized neck edema eed by swelling due to an accumulated by discomfort in the chest unreceded by the sensation of marked discertain of life that cannot be attributed asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention	the lungs, liver, kidney and clottine Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL tition of excessive fluid in the neck Moderate pain; limiting instrumental ADL atted to a heart disorder. Moderate pain; limiting instrumental ADL comfort, distress or agony. - to a CTCAE term associated with Moderate; minimal, local or noninvasive intervention indicated; limiting age-	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities g mechanisms. Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL Severe pain; limiting self care ADL Severe pain; limiting self care ADL - n Grade 5. Severe or medically significant but not immediately life- threatening; hospitalization or	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic acidosis) - - Life-threatening consequences;	Death
Multi-organ failure Definition: A disorder characteriz Neck edema Definition: A disorder characteriz Non-cardiac chest pain Definition: A disorder characteriz Pain Definition: A disorder characteriz Sudden death NOS Definition: An unexpected cessa General disorders and administration site conditions -	ted by progressive deterioration of Asymptomatic localized neck edema and by swelling due to an accumulated by discomfort in the chest unreleading by the sensation of marked discomplete of the complete of	the lungs, liver, kidney and clottine Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL tition of excessive fluid in the neck Moderate pain; limiting instrumental ADL ated to a heart disorder. Moderate pain; limiting instrumental ADL comfort, distress or agony. - to a CTCAE term associated with Moderate; minimal, local or noninvasive intervention	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities g mechanisms. Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL Severe pain; limiting self care ADL Severe pain; limiting self care ADL - a Grade 5. Severe or medically significant but not immediately life-	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic acidosis) - - Life-threatening consequences;	Death

Grade								
Adverse Event	1	2	3	4	5			
Bile duct stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; IV fluids indicated <24 hrs	Severely altered GI function; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characteri	' zed by a narrowing of the lumen of	the bile duct.	1	'	•			
Biliary fistula	-	Symptomatic and intervention not indicated	Severely altered GI function; TPN indicated; endoscopic intervention indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characteri	zed by an abnormal communicatio	n between the bile ducts and anot	her organ or anatomic site.	•	•			
Cholecystitis	-	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characteri	່ zed by inflammation involving the ເ	jallbladder. It may be associated v	vith the presence of gallstones.	1	i			
Gallbladder fistula	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Symptomatic or severely altered GI function; TPN indicated; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characteri	zed by an abnormal communication	n between the gallbladder and and	other organ or anatomic site.					
Gallbladder necrosis	-	-	-	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death			
Definition: A disorder characteri	zed by a necrotic process occurring	g in the gallbladder.	· 					
Gallbladder obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; IV fluids indicated <24 hrs	Symptomatic and severely altered GI function; tube feeding, TPN or hospitalization indicated; non-emergent operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Gallbladder pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care	-	-			
Definition: A disorder characteri	zed by a sensation of marked disco	omfort in the gallbladder region.		'				
Gallbladder perforation	-	-	-	Life-threatening consequences; urgent intervention indicated	Death			
	zed by a rupture in the gallbladder	wall.	T	T	1			
Hepatic failure	-	-	Asterixis; mild encephalopathy; limiting self care ADL	Moderate to severe encephalopathy; coma; life-threatening consequences	Death			
	zed by the inability of the liver to m	etabolize chemicals in the body. L	aboratory test results reveal abnor	mal plasma levels of ammonia, bi	lirubin, la			
dehydrogenase, and alkaline ph Hepatic hemorrhage	Mild; intervention not indicated	Symptomatic; medical intervention indicated	Transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteri	zed by bleeding from the liver.	1	1	9	Į.			
Hepatic necrosis	-	-	-	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death			
Definition: A disorder characteri	l zed by a necrotic process occurring	in the hepatic parenchyma.	1	1	ı			
Hepatic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characteri	zed by a sensation of marked disco	omfort in the liver region.	1					
		·	i .	i .	Death			

	Hepatobiliary disorders									
		Grade								
Adverse Event	1	2	3	4	5					
Portal hypertension	-	Decreased portal vein flow	Reversal/retrograde portal vein flow; associated with varices and/or ascites	Life-threatening consequences; urgent intervention indicated	Death					
Definition: A disorder characterize	ed by an increase in blood pressu	re in the portal venous system.								
Portal vein thrombosis	-	Intervention not indicated	Medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death					
Definition: A disorder characterize	ed by the formation of a thrombus	(blood clot) in the portal vein.								
Hepatobiliary disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated;	Life-threatening consequences; urgent intervention indicated	Death					
			disabling; limiting self care ADL							

		Immune system dis	orders		
			Grade		
Adverse Event	1	2	3	4	5
Allergic reaction	Transient flushing or rash, drug fever <38 degrees C (<100.4 degrees F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
	zed by an adverse local or general	response from exposure to an alle			I
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
	zed by an acute inflammatory react resents with breathing difficulty, di				ypersensitivi
Autoimmune disorder					Dooth
Autoimmune disorder	Asymptomatic; serologic or other evidence of autoimmune reaction, with normal organ function; intervention not indicated	Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism)	Autoimmune reactions involving major organ (e.g., colitis, anemia, myocarditis, kidney)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder resulting fr	om loss of function or tissue destru	iction of an organ or multiple orga	ns, arising from humoral or cellula	r immune responses of the individe	ual to his ow
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilatory support indicated	Death
Definition: A disorder characterize	red by nausea, headache, tachyca	rdia, hypotension, rash, and shorti	ness of breath; it is caused by the	release of cytokines from the cells	i.
Serum sickness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate arthralgia; fever, rash, urticaria, antihistamines indicated	Severe arthralgia or arthritis; extensive rash; steroids or IV fluids indicated	Life-threatening consequences; pressor or ventilatory support indicated	Death
	red by a delayed-type hypersensiti e foreign antigen. Symptoms inclu				
Immune system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

		Infections and infes	tations		
			Grade		
Adverse Event	1	2	3	4	5
Abdominal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	erized by an infectious process invol	ving the abdominal cavity.			
Anorectal infection	Localized; local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	erized by an infectious process invol	ving the anal area and the rectum.		l :f- thti	D41-
Appendicitis	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	erized by acute inflammation to the v	vermiform appendix caused by a pa			
Appendicitis perforated	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	rized by acute inflammation to the viceal wall rupture causes the releas				ıne
Arteritis infective	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	erized by an infectious process invol	ving an artery.	_	1	
Biliary tract infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	rized by an infectious process invol	ving the biliary tract.			
Bladder infection	-	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	rized by an infectious process invol	ving the bladder.			
Bone infection			IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	erized by an infectious process invol	ving the bones.		1	
Breast infection		Local infection with moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	Severe infection; axillary adenitis; IV antibacterial, antifungal, or antiviral intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Bronchial infection	erized by an infectious process invol	1	IV antibiotic antifungal or	Life threatening consequences:	Death
BIOTICIIAI IITECIIOTI		Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	erized by an infectious process invol	ving the bronchi.			
Catheter related infection	-	Localized; local intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	rized by an infectious process that	arises secondary to catheter use.	1	1	
Cecal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

		Infections and infes	Grade		
Adverse Event	1	2	3	4	5
	ed by an infectious process involv		, and the second	7	
Cervicitis infection	ed by an intections process involv	Localized; local intervention	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
Cervicius irriection		indicated (e.g., topical antibiotic,	antiviral intervention indicated;	urgent intervention indicated	Death
		antifungal, or antiviral)	radiologic or operative	g	
			intervention indicated		
Definition: A disorder characterize	ed by an infectious process involv	ing the uterine cervix.			
Conjunctivitis infective	-	Localized; local intervention	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
		indicated (e.g., topical antibiotic,	antiviral intervention indicated;	urgent intervention indicated	
		antifungal, or antiviral)	radiologic or operative		
			intervention indicated	1	l
	ed by an infectious process involv		· ·		1
Corneal infection	-	Localized; local intervention	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
		indicated (e.g., topical antibiotic, antifungal, or antiviral)	antiviral intervention indicated; radiologic or operative	urgent intervention indicated	
		a	intervention indicated		
Definition: A disorder characterize	। ed by an infectious process involv	ing the cornea.	1	1	1
Cranial nerve infection	-	-	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
			antiviral intervention indicated;	urgent intervention indicated	
			radiologic or operative		
			intervention indicated		
Definition: A disorder characterize	ed by an infectious process involv	ing a cranial nerve.			1
Device related infection	-	-	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
			antiviral intervention indicated;	urgent intervention indicated	
			radiologic or operative		
			intervention indicated	1	l
	ed by an infectious process involv	I	T	I	I
Duodenal infection	-	Moderate symptoms; medical	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
		intervention indicated (e.g., oral antibiotics)	antiviral intervention indicated; radiologic or operative	urgent intervention indicated	
			intervention indicated		
Definition: A disorder characterize	ed by an infectious process involv	ing the duodenum.	'	•	•
Encephalitis infection	-	-	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
			antiviral intervention indicated;	urgent intervention indicated	
			severe changes in mental		
			status; self-limited seizure		
			activity; focal neurologic		
5 6 W A P 1 1 4 4 5			abnormalities		
	ed by an infectious process involv	ing the brain tissue.	ny erie er		l
Encephalomyelitis infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated;	Life-threatening consequences; urgent intervention indicated	Death
			radiologic or operative	argoni intervention indicated	
			intervention indicated		
Definition: A disorder characterize	ed by an infectious process involv	ing the brain and spinal cord tissu	es.	•	•
Endocarditis infective		-	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
			antiviral intervention indicated;	urgent intervention indicated	
			radiologic or operative		
			intervention indicated		
3 C 10 A 10 I I I I I	ed by an infectious process involv	ing the endocardial layer of the he	art.		
Definition: A disorder characterize					
Definition: A disorder characterize	-	Local intervention indicated	Systemic intervention or	Blindness (20/200 or worse)	-

			Grade						
Adverse Event	1	2	3	4	5				
Enterocolitis infectious	•	Passage of >3 unformed stools	IV antibiotic, antifungal, or	Life-threatening consequences;	Death				
Enterocontis infectious	-	per 24 hrs or duration of illness	antiviral intervention indicated;	urgent intervention indicated	Dealli				
		l'	· ·	digent intervention indicated					
		>48 hrs; moderate abdominal	radiologic, endoscopic, or						
		pain	operative intervention indicated;						
			profuse watery diarrhea with						
			signs of hypovolemia; bloody						
			diarrhea; fever; severe						
			abdominal pain; hospitalization						
			indicated						
Definition: A disorder characteriz	red by an infectious process involv	ing the small and large intestines.	ı	ı	1				
Sophageal infection	T ₋	Local intervention indicated	IV antibiotic, antifungal, or	Life-threatening consequences;	Death				
.sepriagear iniceneri		(e.g., oral antibiotic, antifungal,	antiviral intervention indicated;	urgent intervention indicated	2000				
				argent intervention indicated					
		antiviral)	radiologic or operative						
	1		intervention indicated	l					
efinition: A disorder characteriz	red by an infectious process involv	ing the esophagus.	T	T					
Eye infection	-	Localized; local intervention	IV antibiotic, antifungal, or	Life-threatening consequences;	Death				
		indicated (e.g., topical antibiotic,	antiviral intervention indicated;	urgent intervention indicated;					
		antifungal, or antiviral)	radiologic or operative	enucleation					
		,	intervention indicated						
Definition: A disorder characterize	। ed by an infectious process involv	ing the eve	1	ı	1				
	Sa Sy an iniconous process involv	ing the eye.	IV antibiotic antifunction	Life threatening con	Dogu				
Gallbladder infection	1-	-	IV antibiotic, antifungal, or	Life-threatening consequences;	Death				
			antiviral intervention indicated;	urgent intervention indicated					
			radiologic, endoscopic, or						
			operative intervention indicated						
Definition: A disorder characteriz	ed by an infectious process involv	ing the gallbladder.							
Gum infection	Local therapy indicated (swish	Moderate symptoms; oral	IV antibiotic, antifungal, or	Life-threatening consequences;	Death				
	and swallow)	intervention indicated (e.g.,	antiviral intervention indicated;	urgent intervention indicated					
	<i>'</i>	antibiotic, antifungal, antiviral)	radiologic or operative	"					
		a	intervention indicated						
Definition: A disorder characteris	l ed by an infectious process involv	ing the gums	1	I	ı				
	led by all illiections process litvolv	ing the guins.	N/		D41-				
Hepatic infection	-	-	IV antibiotic, antifungal, or	Life-threatening consequences;	Death				
			antiviral intervention indicated;	urgent intervention indicated					
			radiologic or operative						
			intervention indicated						
Definition: A disorder characteriz	ed by an infectious process involv	ing the liver.	1	I					
Hepatitis viral	Asymptomatic, treatment not	-	Symptomatic liver dysfunction;	Decompensated liver function	Death				
	indicated		fibrosis by biopsy; compensated	(e.g., ascites, coagulopathy,					
			cirrhosis; reactivation of chronic	encephalopathy, coma)					
			hepatitis	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,					
Definition: A disorder characteriz	। ed by a viral pathologic process in	volving the liver parenchyma	1 .	!	1				
		1	IV antibiotic antifuncel or	Life threatening consequences:	Death				
Infective myositis	1-	Localized; local intervention	IV antibiotic, antifungal, or	Life-threatening consequences;	Death				
		indicated (e.g., topical antibiotic,	antiviral intervention indicated;	urgent intervention indicated					
		antifungal, or antiviral)	radiologic or operative						
			intervention indicated						
Definition: A disorder characteriz	ed by an infectious process involv	ing the skeletal muscles.	T						
Joint infection	-	Localized; local intervention	Arthroscopic intervention	Life-threatening consequences;	Death				
		indicated; oral intervention	indicated (e.g., drainage) or	urgent intervention indicated					
		indicated (e.g., antibiotic,	arthrotomy (e.g., open surgical						
		antifungal, antiviral); needle	drainage)						
		aspiration indicated (single or	"						
		multiple)							
Definition: A disorder characterize	। ed by an infectious process involv	1	1	I	1				
	.ou by an inicollous process involv	ing a joint.	N/ antibiatio	Life threatering	D"				
Kidney infection	-	-	IV antibiotic, antifungal, or	Life-threatening consequences;	Death				
			antiviral intervention indicated;	urgent intervention indicated					
			radiologic, endoscopic, or						
			radiologic, endoscopic, or operative intervention indicated						

		Infections and infes			
			Grade		
Adverse Event	1	2	3	4	5
Laryngitis	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder charac	terized by an inflammatory process	involving the larynx.		1	
Lip infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	-	-
Definition: A disorder charac	terized by an infectious process invo	olving the lips.		_	
Lung infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder charac	terized by an infectious process invo	olving the lungs.			
Lymph gland infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder charac	terized by an infectious process invo	olving the lymph nodes.	T	1	
Mediastinal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder charac	terized by an infectious process invo	olving the mediastinum.			
Meningitis	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated; focal neurologic deficit	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder charac	terized by acute inflammation of the	meninges of the brain and/or spinal	cord.	1	,
Mucosal infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder charac	terized by an infectious process invo	olving a mucosal surface.		1	
Nail infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	-	-
Definition: A disorder charac	terized by an infectious process invo	olving the nail.		1	
Otitis externa	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
		olving the outer ear and ear canal. C	•	ive water exposure (swimmer's ea	r infection
Otitis media	-	Localized; local intervention	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
out mout		indicated (e.g., topical antibiotic, antifungal, or antiviral)		urgent intervention indicated	Journ
Definition: A disorder charac	terized by an infectious process invo	olving the middle ear.		1	
Ovarian infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative	Life-threatening consequences; urgent intervention indicated	Death

		Infections and infes	tations		
			Grade		
Adverse Event	1	2	3	4	5
Pancreas infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	erized by an infectious process involv	ing the pancreas.			
Papulopustular rash	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; lifethreatening consequences	Death
	erized by an eruption consisting of pa				o, and upper
	this rash does not present with whiteh		i i	esions.	
Paronychia	Nail fold edema or erythema; disruption of the cuticle	Localized intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	Surgical intervention or IV antibiotics indicated; limiting self care ADL	-	-
Definition: A disorder characte	erized by an infectious process involvi	ing the soft tissues around the nai	l		
Pelvic infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder character	erized by an infectious process involving	ing the pelvic cavity.	1	<u> </u>	
Penile infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	erized by an infectious process involvi	ing the penis.			
Periorbital infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	erized by an infectious process involvi		N/	if_	D41-
Peripheral nerve infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	erized by an infectious process involvi	ing the peripheral nerves.		l .	
Peritoneal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder character	erized by an infectious process involvi	ing the peritoneum.	1		
Pharyngitis	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder character	erized by inflammation of the throat.	· 			
Phlebitis infective	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

Definition: A disorder characterized by an infectious process involving the vein. Clinical manifestations include erythema, marked discomfort, swelling, and induration along the coff the infection Localized; local intervention indicated; antifungal, or antivarial intervention indicated. Definition: A disorder characterized by an infectious process involving the pleura. Producted by an infectious process involving the prostate gland. Rash pushular Life-threatening consequences; antibiotic, antifungal, antiviral) antiviral intervention indicated (e.g., antibiotic, antifungal, or antiviral) antiviral intervention indicated (e.g., antibiotic, antifungal, or antiviral) Definition: A disorder characterized by an infectious process involving the prostate gland. Rash pushular Vanibiotic, antifungal, or antiviral) Vanibiotic, antifungal, or antiviral intervention indicated (e.g., appearal antibiotic, antifungal, or antiviral) Vanibiotic, antifungal, or antiviral intervention indicated (e.g., appearal antibiotic, antifungal, or antiviral) Vanibiotic, antifungal, or antiviral intervention indicated (e.g., appearal antibiotic, antifungal, or antiviral) Vanibiotic, antifungal, or antiviral intervention indicated (e.g., antibiotic, antifungal, or antiviral) Vanibiotic, antifungal, or antiviral intervention indicated (e.g., antibiotic, antifungal, or antiviral) Vanibiotic, antifungal, or antiviral intervention indicated Vanibiotic, antifungal, or antiviral Vanibiotic, a			Infections and infest	tations		
Definition: A disorder characterized by an infectious process involving the vein. Clinical manifestations include erythema, marked discomfort, swelling, and induration along the of the infected vein. Localized, local intervention indicated, antifungal, or antiviral intervention indicated, antifungal, or antiviral intervention indicated upper intervention indicated. The comparative intervention indicated antifungal, antiviral) Definition: A disorder characterized by an infectious process involving the prostate gland. Rash postular -				Grade		
Peural infection - Localized; local intervention indicated, antifungal, or antiviral) process involving the pleura. Definition: A disorder characterized by an infectious process involving the pleura. Definition: A disorder characterized by an infectious process involving the pleura. Definition: A disorder characterized by an infectious process involving the prostate gland. Reach pushlatr Definition: A disorder characterized by an infectious process involving the prostate gland. Reach pushlatr Definition: A disorder characterized by an infectious process involving the prostate gland. Reach pushlatr Definition: A disorder characterized by an infectious process involving the inference of the prostate gland. Reach pushlatr Definition: A disorder characterized by an infectious process involving the assal mucosal. Definition: A disorder characterized by an infectious process involving the salivary gland infection Definition: A disorder characterized by an infectious process involving the salivary gland. Definition: A disorder characterized by an infectious process involving the salivary gland. Definition: A disorder characterized by an infectious process involving the salivary gland. Definition: A disorder characterized by an infectious process involving the salivary gland. Definition: A disorder characterized by an infectious process involving the salivary gland. Definition: A disorder characterized by an infectious process involving the salivary gland. Definition: A disorder characterized by an infectious process involving the scrotum. Sepsis Definition: A disorder characterized by an infectious process involving the scrotum. Sepsis Definition: A disorder characterized by an infectious process involving the mucous membranes of the paramasal sinuses. Definition: A disorder characterized by an infectious process involving the mucous membranes of the paramasal sinuses. Sin infection Localized, local intervention indicated (e.g., inpoint antifungal, or antiviral) indicated (e.g. poperal antifu	Adverse Event	1	2	3	4	5
Indicated (i.g., popied antibiotic, antifurgal, or antibiration . Definition: A disorder characterized by an infectious process involving the acround indicated (i.g., popied antibiration indicated		ed by an infectious process involvi	ng the vein. Clinical manifestation	s include erythema, marked disco	mfort, swelling, and induration alo	ng the course
Prostate infection			indicated (e.g., topical antibiotic, antifungal, or antiviral)	antiviral intervention indicated; radiologic, endoscopic, or		Death
Intervention indicated (e.g., antitivation, antitivarial,		ed by an infectious process involvi				- "
Rash pustular - Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral) Definition: A disorder characterized by a circumscribed and elevated skin lesion filled with pus. Ribinitis infective - Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral) Definition: A disorder characterized by an infectious process involving the nasal mucosal. Salivary gland infection - Intervention indicated (e.g., antibiotic, antifungal, or antiviral) Definition: A disorder characterized by an infectious process involving the salivary gland. Scrotal infection - Localized; local intervention indicated (e.g., antibiotic, antifungal, or antiviral intervention indicated: antiviral) Definition: A disorder characterized by an infectious process involving the salivary gland. Scrotal infection - Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral intervention indicated: artifungal, or antiviral intervention indicated: antifungal, or antiviral intervention indicated: antiviral intervention indica	Prostate infection	-	intervention indicated (e.g.,	antiviral intervention indicated; radiologic, endoscopic, or		Death
Definition: A disorder characterized by a circumscribed and elevated skin lesion filled with pus.	Definition: A disorder characterize	ed by an infectious process involvi	ng the prostate gland.			
Rhinitis infective	Rash pustular	-	indicated (e.g., topical antibiotic,	antiviral intervention indicated; radiologic or operative	-	-
Indicated (e.g., topical antiblotic, antifungal, or antiviral)	Definition: A disorder characterize	ed by a circumscribed and elevate	d skin lesion filled with pus.			
Salivary gland infection Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral intervention indicated: radiologic or operative intervention indicated (e.g., antifungal, or antiviral) Moderate (e.g., topical antibiotic, antifungal, or antiviral) Moderate value (e.g., antibiotic, antifungal, or antiviral) Moder	Rhinitis infective	-	indicated (e.g., topical antibiotic,	-	-	-
intervention indicated (e.g., antifungal, antiviral) antiviral intervention indicated; radiologic or operative intervention indicated intervention indicated. Scrotal infection - Localized, local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral) indicated (e.g., topical antibiotic, antifungal, or antiviral) Definition: A disorder characterized by an infectious process involving the scrotum. Sepsis Localized, local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral) Definition: A disorder characterized by an infectious process involving the scrotum. Sepsis Localized, local intervention indicated intervention indicated (e.g., topical antibiotic, antifungal, or antiviral) Definition: A disorder characterized by the presence of pathogenic microorganisms in the blood stream that cause a rapidly progressing systemic reaction that may lead to shock indicated (e.g., topical antibiotic, antifungal, or antiviral) Definition: A disorder characterized by an infectious process involving the mucous membranes of the paranasal sinuses. Skin infection Localized, local intervention indicated (e.g., antibiotic, antifungal, or antiviral) Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral) Definition: A disorder characterized by an infectious process involving the mucous membranes of the paranasal sinuses. Skin infection Localized, local intervention indicated (e.g., antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention ind	Definition: A disorder characterize	ed by an infectious process involvi	ng the nasal mucosal.		Γ	
Scrotal infection Cocalized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral) intervention indicated; antifungal, or antiviral intervention indicated; antifungal, or antiviral intervention indicated; andiologic or operative intervention indicated Definition: A disorder characterized by an infectious process involving the scrotum. Sepsis	Salivary gland infection	-	intervention indicated (e.g.,	antiviral intervention indicated; radiologic or operative		Death
indicated (e.g., topical antibiotic, antifungal, or antiviral) Definition: A disorder characterized by an infectious process involving the scrotum. Sepsis Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or indicated (e.g., topical antibiotic, antifungal, or antiviral) Definition: A disorder characterized by the presence of pathogenic microorganisms in the blood stream that cause a rapidly progressing systemic reaction that may lead to shood indicated (e.g., topical antibiotic, antifungal, or indicated (e.g., topical antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated indicated (e.g., antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated (e.g., antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated; radiologic or operat	Definition: A disorder characterize	ed by an infectious process involvi	ng the salivary gland.			
Sepsis Life-threatening consequences; Death urgent intervention indicated by the presence of pathogenic microorganisms in the blood stream that cause a rapidly progressing systemic reaction that may lead to shock Sinusitis - Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral) IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated urgent i	Scrotal infection	-	indicated (e.g., topical antibiotic,	antiviral intervention indicated; radiologic or operative		Death
Definition: A disorder characterized by the presence of pathogenic microorganisms in the blood stream that cause a rapidly progressing systemic reaction that may lead to shoot shoot stream that cause a rapidly progressing systemic reaction that may lead to shoot shoot shoot stream that cause a rapidly progressing systemic reaction that may lead to shoot shoot shoot shoot shoot stream that cause a rapidly progressing systemic reaction that may lead to shoot s	Definition: A disorder characterize	ed by an infectious process involvi	ng the scrotum.			
Sinusitis Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated (e.g., topical antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated Definition: A disorder characterized by an infectious process involving the mucous membranes of the paranasal sinuses. Skin infection	Sepsis	-	-	-		Death
indicated (e.g., topical antibiotic, antifungal, or antiviral) Definition: A disorder characterized by an infectious process involving the mucous membranes of the paranasal sinuses. Skin infection Localized, local intervention indicated (e.g., antibiotic, antifungal, antiviral) Definition: A disorder characterized by an infectious process involving the mucous membranes of the paranasal sinuses. Skin infection Localized, local intervention indicated (e.g., antibiotic, antifungal, antiviral) Definition: A disorder characterized by an infectious process involving the skin. Small intestine infection Moderate symptoms; oral intervention indicated; radiologic or operative intervention indicated.	Definition: A disorder characterize	ed by the presence of pathogenic	microorganisms in the blood strea	m that cause a rapidly progressing	g systemic reaction that may lead	to shock.
Skin infection Localized, local intervention indicated (e.g., antifungal, antiviral) Definition: A disorder characterized by an infectious process involving the skin. Small intestine infection - Moderate symptoms; oral intervention indicated (e.g., antifungal, antiviral) Moderate symptoms; oral intervention indicated; antiviral intervention indicated; antiviral intervention indicated; radiologic or operative intervention indicated	Sinusitis	1	indicated (e.g., topical antibiotic,	antiviral intervention indicated; radiologic, endoscopic, or		Death
indicated antibiotic, antifungal, antiviral) antiviral intervention indicated; radiologic or operative intervention indicated Definition: A disorder characterized by an infectious process involving the skin. Small intestine infection - Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral) IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated intervention indicated (e.g., antibiotic, antifungal, antiviral) IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Definition: A disorder characterize	ed by an infectious process involvi	ng the mucous membranes of the	paranasal sinuses.		
Small intestine infection - Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral) Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral) IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Skin infection	· ·		antiviral intervention indicated; radiologic or operative		Death
intervention indicated (e.g., antiviral intervention indicated; antibiotic, antifungal, antiviral) antiviral intervention indicated; antiviral intervention indicated intervention indicated.	Definition: A disorder characterize	ed by an infectious process involvi	ng the skin.	T	T	
L	Small intestine infection	-	intervention indicated (e.g.,	antiviral intervention indicated; radiologic or operative		Death
Definition: A disorder characterized by an infectious process involving the small intestine.	Definition: A disorder characterize	ed by an infectious process involvi	ng the small intestine.			
Soft tissue infection - Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated Life-threatening consequences; urgent intervention indicated radiologic or operative intervention indicated		-	indicated (e.g., topical antibiotic, antifungal, or antiviral)	antiviral intervention indicated; radiologic or operative	- '	Death
Definition: A disorder characterized by an infectious process involving soft tissues.		ed by an infectious process involvi	ng soft tissues.		I	
Splenic infection - IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Splenic infection	-	-	antiviral intervention indicated; radiologic or operative		Death

		Infections and infes			
			Grade		1
Adverse Event	1	2	3	4	5
Definition: A disorder characteri	ized by an infectious process involv	ing the spleen.	1	1	
Stoma site infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteri	ized by an infectious process involv	ing a stoma (surgically created op	ening on the surface of the body).		,
Tooth infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteri	ized by an infectious process involv	ing a tooth.	1	1	
Tracheitis	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	ized by an infectious process involv	T			Ī
Upper respiratory infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteri	zed by an infectious process involv	ing the upper respiratory tract (nos	se, paranasal sinuses, pharynx, la	rynx, or trachea).	1
Urethral infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteri	zed by an infectious process involv	ing the urethra.			
Urinary tract infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteri	ized by an infectious process involv	ing the urinary tract, most commo	nly the bladder and the urethra.		
Uterine infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteri	ized by an infectious process involv	ing the endometrium. It may exten	d to the myometrium and parame	trial tissues.	
Vaginal infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteri	zed by an infectious process involv	ing the vagina.			
Vulval infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteri	ized by an infectious process involv	ing the vulva.			
Nound infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteri	ized by an infectious process involv	ing the wound.	T	T	
nfections and infestations - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

	J,	, poisoning and procedu	Grade		
Adverse Event	1	2	3	4	5
Ankle fracture	Mild; non-surgical intervention	Limiting instrumental ADL;	Limiting self care ADL; elective	- -	_
	indicated	operative intervention indicated	surgery indicated		
Definition: A finding of damage to Iffected leg and foot.	o the ankle joint characterized by a	a break in the continuity of the ank	le bone. Symptoms include marke	d discomfort, swelling and difficult	y moving th
Aortic injury	-	-	Severe symptoms; limiting self	Life-threatening consequences;	Death
			care ADL; disabling; repair or revision indicated	evidence of end organ damage; urgent operative intervention indicated	
Definition: A finding of damage to	o the aorta.	!	!	I	ļ
Arterial injury	Asymptomatic diagnostic	Symptomatic (e.g.,	Severe symptoms; limiting self	Life-threatening consequences;	Death
	finding; intervention not indicated	claudication); repair or revision not indicated	care ADL; disabling; repair or revision indicated	evidence of end organ damage; urgent operative intervention indicated	
Definition: A finding of damage to	o an artery.	I	I	ı	ı
Biliary anastomotic leak	Asymptomatic diagnostic	Symptomatic; medical	Severe symptoms; radiologic,	Life-threatening consequences;	Death
	observations only; intervention	intervention indicated	endoscopic or elective operative	urgent operative intervention	
	not indicated		intervention indicated	indicated	
	f bile due to breakdown of a biliary				
Bladder anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage o	f urine due to breakdown of a blad	der anastomosis (surgical connec	tion of two separate anatomic stru	ctures).	1
Bruising	Localized or in a dependent area	Generalized	-	-	-
Definition: A finding of injury of the	ne soft tissues or bone characteriz	ed by leakage of blood into surrou	nding tissues.	T	
Burn	Minimal symptoms; intervention not indicated	Medical intervention; minimal debridement indicated	Moderate to major debridement or reconstruction indicated	Life-threatening consequences	Death
• .	integrity to the anatomic site of an depends on the length and intensi		• •	nicals, direct heat, electricity, flame	es and
Dermatitis radiation	Faint erythema or dry	Moderate to brisk erythema;	Moist desquamation in areas	Life-threatening consequences;	Death
	desquamation	patchy moist desquamation,	other than skin folds and	skin necrosis or ulceration of full	
		mostly confined to skin folds	creases; bleeding induced by	thickness dermis; spontaneous	
		and creases; moderate edema	minor trauma or abrasion	bleeding from involved site; skin graft indicated	
Definition: A finding of cutaneous	। s inflammatory reaction occurring a	। as a result of exposure to biologica	। allv effective levels of ionizing radia	19	1
Esophageal anastomotic leak	Asymptomatic diagnostic	Symptomatic; medical	Severe symptoms; radiologic,	Life-threatening consequences;	Death
	observations only; intervention not indicated	intervention indicated	endoscopic or elective operative intervention indicated	urgent operative intervention indicated	
Definition: A finding of leakage d	ue to breakdown of an esophagea	l anastomosis (surgical connection	of two separate anatomic structu	res).	
Fall	Minor with no resultant injuries; intervention not indicated	Symptomatic; noninvasive intervention indicated	Hospitalization indicated	-	-
Definition: A finding of sudden m	ovement downward, usually result	ing in injury.			
Fallopian tube anastomotic leak	Asymptomatic; clinical or diagnostic observations only;	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative	Life-threatening consequences; urgent operative intervention	Death
	intervention not indicated		intervention indicated	indicated	
Definition: A finding of leakage d	ue to breakdown of a fallopian tub	e anastomosis (surgical connectio	n of two separate anatomic structu	ıres).	
Fallopian tube perforation	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated (e.g., organ resection)	Death
Definition: A finding of rupture of	the fallopian tube wall.				
Fracture	Asymptomatic; clinical or	Symptomatic but non-displaced;	Severe symptoms; displaced or	Life-threatening consequences;	Death
	diagnostic observations only; intervention not indicated	immobilization indicated	open wound with bone exposure; disabling; operative	urgent intervention indicated	

	, wi y	, poisoning and procedu	Grade		
Adverse Event	1	2	3	4	5
Gastric anastomotic leak	Asymptomatic diagnostic observations only; intervention	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative	Life-threatening consequences; urgent operative intervention	Death
	not indicated	Intervention indicated	intervention indicated	indicated	
Deficialization of localization of	1	 +	•	Indicated	l
		tomosis (surgical connection of tw		T	I
Gastrointestinal anastomotic	Asymptomatic diagnostic	Symptomatic; medical	Severe symptoms; radiologic,	Life-threatening consequences;	Death
leak	observations only; intervention	intervention indicated	endoscopic or elective operative	urgent operative intervention	
	not indicated	I	intervention indicated	indicated	
Definition: A finding of leakage d	ue to breakdown of a gastrointesti	nal anastomosis (surgical connect	tion of two separate anatomic struc	ctures).	
Gastrointestinal stoma necrosis	-	Superficial necrosis;	Severe symptoms;	Life-threatening consequences;	Death
		intervention not indicated	hospitalization or elective	urgent intervention indicated	
			operative intervention indicated		
Definition: A finding of a necrotic	process occurring in the gastroint	estinal tract stoma.			
Hip fracture	-	Hairline fracture; mild pain;	Severe pain; hospitalization or	Life-threatening consequences;	-
		limiting instrumental ADL; non-	intervention indicated for pain	symptoms associated with	
		surgical intervention indicated	control (e.g., traction); operative	neurovascular compromise	
			intervention indicated		
Definition: A finding of traumatic	injury to the hip in which the conti	nuity of either the femoral head, fe	moral neck, intertrochanteric or su	btrochanteric regions is broken.	
Injury to carotid artery	_	_	Severe symptoms; limiting self	Life-threatening consequences;	Death
, .,			care ADL (e.g., transient	urgent intervention indicated	
			cerebral ischemia); repair or	- I I I I I I I I I I I I I I I I I I I	
			revision indicated		
Definition: A finding of damage to	the carotid artery.	1	1	I	•
Injury to inferior vena cava				Life threatening concequences:	Death
injury to intenor vena cava	-	-	-	Life-threatening consequences; urgent intervention indicated	Dealii
D 6 12 A 6 12 A 6 1			I	argent intervention indicated	l
Definition: A finding of damage to	the interior vena cava.	1		Τ	1
Injury to jugular vein	-	-	Symptomatic limiting self care	Life-threatening consequences;	Death
			ADL; disabling; repair or	urgent intervention indicated	
	I	I	revision indicated	I	l
Definition: A finding of damage to	the jugular vein.	1	1	T	
Injury to superior vena cava	Asymptomatic diagnostic	Symptomatic; repair or revision	Severe symptoms; limiting self	Life-threatening consequences;	Death
	finding; intervention not	not indicated	care ADL; disabling; repair or	evidence of end organ damage;	
	indicated		revision indicated	urgent operative intervention	
			1	indicated	
Definition: A finding of damage to	the superior vena cava.				
Intestinal stoma leak	Asymptomatic diagnostic	Symptomatic; medical	Severe symptoms; radiologic,	Life-threatening consequences;	Death
	observations only; intervention	intervention indicated	endoscopic or elective operative	urgent operative intervention	
	not indicated		intervention indicated	indicated	
Definition: A finding of leakage of	f contents from an intestinal stoma	a (surgically created opening on th	e surface of the body).		
Intestinal stoma obstruction	-	Self-limited; intervention not	Severe symptoms; IV fluids,	Life-threatening consequences;	Death
		indicated	tube feeding, or TPN indicated	urgent operative intervention	
			>=24 hrs; elective operative	indicated	
			intervention indicated		
Definition: A finding of blockage	of the normal flow of the contents	of the intestinal stoma.	•	•	•
Intestinal stoma site bleeding	Minimal bleeding identified on	Moderate bleeding; medical	Severe bleeding; transfusion	Life-threatening consequences;	Death
mostinai stoma site biecuilly	clinical exam; intervention not	intervention indicated	indicated; radiologic or	urgent intervention indicated	Doani
	indicated		endoscopic intervention	a.g.s.ik intorvontion indicated	
			indicated		
Definition: A finding of blood leak	age from the intestinal stoma	1	1	I	1
		D 01 0 01 1	0 11 "	Lee al	D .:
Intraoperative arterial injury	Primary repair of injured	Partial resection of injured	Complete resection or	Life-threatening consequences;	Death
	organ/structure indicated	organ/structure indicated	reconstruction of injured	urgent intervention indicated	
			organ/structure indicated;		
.	l		disabling	I	I
Definition: A finding of damage to	o an artery during a surgical proce	dure.		<u> </u>	
Intraoperative breast injury	Primary repair of injured	Partial resection of injured	Complete resection or	Life-threatening consequences;	Death
	organ/structure indicated	organ/structure indicated	reconstruction of injured	urgent intervention indicated	
	į.	ĺ	lorgon/structure indicated:	İ	1
			organ/structure indicated; disabling		

	,,	, poisoning and proced	Grade		
Adverse Event	1	2	3	4	5
	o the breast parenchyma during a		•	•	
Intraoperative cardiac injury	-	-	Primary repair of injured organ/structure indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to	o the heart during a surgical proce	edure.			
Intraoperative ear injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection of injured organ/structure indicated; disabling (e.g., impaired hearing; impaired balance)	Life-threatening consequences; urgent intervention indicated	Death
	o the ear during a surgical proced				I
Intraoperative endocrine injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to	o the endocrine gland during a sui	rgical procedure.			
Intraoperative gastrointestinal injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to	o the gastrointestinal system durin	g a surgical procedure.			
Intraoperative head and neck injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to	o the head and neck during a surg	ical procedure.			
Intraoperative hemorrhage	-	-	Postoperative radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of uncontroll	ed bleeding during a surgical proc	edure.	ı	!	•
Intraoperative hepatobiliary injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to	o the hepatic parenchyma and/or	biliary tract during a surgical pro	cedure.		
Intraoperative musculoskeletal injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to	o the musculoskeletal system duri	ng a surgical procedure.			
Intraoperative neurological injury	Primary repair of injured organ/structure indicated of the nervous system during a sur	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
	Primary repair of injured	Ĭ	Complete resection or	Life threatening concessioned	Dooth
Intraoperative ocular injury	organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to	o the eye during a surgical proced	ure.			
Intraoperative renal injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to	o the kidney during a surgical prod	cedure.			
Intraoperative reproductive tract injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated;	Life-threatening consequences; urgent intervention indicated	Death

	Injury	, poisoning and procedu	ral complications		
			Grade		
Adverse Event	1	2	3	4	5
	o the reproductive organs during a				
Intraoperative respiratory injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to	। o the respiratory system during a s	। surgical procedure.	1 3	ı	1
Intraoperative skin injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to	o the skin during a surgical proced	ure.			
Intraoperative splenic injury	-	Primary repair of injured organ/structure indicated	Resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
	o the spleen during a surgical proc				
Intraoperative urinary injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to	o the urinary system during a surg	ical procedure.		<u> </u>	
Intraoperative venous injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to	o a vein during a surgical procedu	re.		<u> </u>	
Kidney anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage o	f urine due to breakdown of a kidn	ey anastomosis (surgical connecti	on of two separate anatomic struc	tures).	
Large intestinal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage d	ue to breakdown of an anastomos	is (surgical connection of two sepa	arate anatomic structures) in the la	arge intestine.	
Pancreatic anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage d	ue to breakdown of a pancreatic a	nastomosis (surgical connection o	of two separate anatomic structures	s).	
Pharyngeal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage d	ue to breakdown of a pharyngeal	anastomosis (surgical connection	of two separate anatomic structure	es).	
Postoperative hemorrhage	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; radiologic, endoscopic, or operative intervention indicated	Transfusion indicated of >=2 units (10 cc/kg for pediatrics) pRBCs beyond protocol specification; urgent radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of bleeding of	occurring after a surgical procedur	e. T	1		
Postoperative thoracic procedure complication	-	Extubated within 24 - 72 hrs postoperatively	Extubated >72 hrs postoperatively, but before tracheostomy indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
	sly undocumented problem that oc	· ·		I .	
Prolapse of intestinal stoma	Asymptomatic; reducible	Recurrent after manual reduction; local irritation or stool leakage; difficulty to fit appliance; limiting instrumental ADL	Severe symptoms; elective operative intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death

Injury, poisoning and procedural complications								
			Grade					
Adverse Event	1	2	3	4	5			
Definition: A finding of protrusion	of the intestinal stoma (surgically	created opening on the surface of	the body) above the abdominal su	ırface.				
Prolapse of urostomy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Local care or maintenance; minor revision indicated	Dysfunctional stoma; elective operative intervention or major stomal revision indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A finding of displacem	ent of the urostomy.							
Radiation recall reaction (dermatologic)	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death			
Definition: A finding of acute skin	inflammatory reaction caused by	drugs, especially chemotherapeut	ic agents, for weeks or months fol	owing radiotherapy. The inflamma	tory reaction			
is confined to the previously irrad	liated skin and the symptoms disa	ppear after the removal of the pha	rmaceutical agent.	<u> </u>	,			
Rectal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A finding of leakage du	ue to breakdown of a rectal anasto	omosis (surgical connection of two	separate anatomic structures).		,			
Seroma	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; simple aspiration indicated	Symptomatic, elective radiologic or operative intervention indicated	-	-			
Definition: A finding of tumor-like	collection of serum in the tissues.	Т	T	<u></u>				
Small intestinal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A finding of leakage du	ue to breakdown of an anastomos	is (surgical connection of two sepa	arate anatomic structures) in the si	mall bowel.				
Spermatic cord anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A finding of leakage du	ue to breakdown of a spermatic co	ord anastomosis (surgical connecti	on of two separate anatomic struc	tures).				
Spinal fracture	Mild back pain; nonprescription analgesics indicated	Moderate back pain; prescription analgesics indicated; limiting instrumental ADL	Severe back pain; hospitalization or intervention indicated for pain control (e.g., vertebroplasty); limiting self care ADL; disability	Life-threatening consequences; symptoms associated with neurovascular compromise	Death			
Definition: A finding of traumatic i	injury to the spine in which the cor	intinuity of a vertebral bone is broke	en.	!	1			
Stenosis of gastrointestinal stoma	-	Symptomatic; IV fluids indicated <24 hrs; manual dilation at bedside	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A finding of narrowing	of the gastrointestinal stoma (surg	gically created opening on the surf	ace of the body).	<u> </u>	,			
Stomal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	-	-			
Definition: A disorder characterize gastroenterostomy procedure.	ed by a circumscribed, inflammato	ory and necrotic erosive lesion on t	he jejunal mucosal surface close t	to the anastomosis site following a	ı			
Tracheal hemorrhage	Minimal bleeding identified on	Moderate bleeding; medical	Severe bleeding; transfusion	Life-threatening consequences;	Death			
naciea nenomage	clinical or diagnostic exam; intervention not indicated	intervention indicated	indicated; radiologic or endoscopic intervention indicated	urgent intervention indicated	Death			
Definition: A finding of bleeding fr	rom the trachea.	T	I	T	1			
Tracheal obstruction	Partial asymptomatic obstruction on examination (e.g., visual, radiologic or endoscopic)	Symptomatic (e.g., noisy airway breathing), no respiratory distress; medical intervention indicated (e.g., steroids); limiting instrumental ADL	Stridor; radiologic or endoscopic intervention indicated (e.g., stent, laser); limiting self care ADL	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death			
	1	1	1	1	1			

		, poisoning and procedu	Grade		
Adverse Event	1	2	3	4	5
Tracheostomy site bleeding	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of blood lea	kage from the tracheostomy site.	+			
Ureteric anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
	lue to breakdown of a ureteral ana	T T		T .	
Jrethral anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage o	lue to breakdown of a urethral ana	stomosis (surgical connection of tw	vo separate anatomic structures).		
Urostomy leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of	of contents from a urostomy.			Г	
Urostomy obstruction	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; dilation or endoscopic repair or stent placement indicated	Altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); elective operative intervention indicated	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
Definition: A finding of blockage	of the urostomy.	T.			
Urostomy site bleeding	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of bleeding	from the urostomy site.	'	•	•	
Urostomy stenosis	-	Symptomatic but no hydronephrosis, no sepsis or no renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic (e.g., hydronephrosis, or renal dysfunction); elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of narrowing	of the opening of a urostomy.	•			
Uterine anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage o	lue to breakdown of a uterine anas	tomosis (surgical connection of tw	o separate anatomic structures).		
Uterine perforation	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	zed by a rupture in the uterine wall.		0		D41-
/aginal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of	lue to breakdown of a vaginal anas	stomosis (surgical connection of tw	vo separate anatomic structures).	İ	
Vas deferens anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of	lue to breakdown of a vas deferens	s anastomosis (surgical connection	n of two separate anatomic structu	res).	
Vascular access complication	-	Device dislodgement, blockage, leak, or malposition; device replacement indicated	Deep vein or cardiac thrombosis; intervention indicated (e.g., anticoagulation, lysis, filter, invasive procedure)	Embolic event including pulmonary embolism or life-threatening thrombus	Death

	Injury	, poisoning and procedu	ral complications		
			Grade		
Adverse Event	1	2	3	4	5
Venous injury	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); repair or revision not indicated	Severe symptoms; limiting self care ADL; repair or revision indicated; disabling	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to	a vein.				
Wound complication	Incisional separation of <=25% of wound, no deeper than superficial fascia	Incisional separation >25% of wound; local care indicated	Hernia without evidence of strangulation; fascial disruption/dehiscence; primary wound closure or revision by operative intervention indicated	Hernia with evidence of strangulation; major reconstruction flap, grafting, resection, or amputation indicated	Death
· · · · · ·	Incisional separation of <=25%	1	Fascial disruption or dehiscence	Life threatening concessions	Dooth
Wound dehiscence	Incisional separation of <=25% of wound, no deeper than superficial fascia	Incisional separation >25% of wound with local care; asymptomatic hernia or symptomatic hernia without evidence of strangulation	Hascial disruption or deniscence without evisceration; primary wound closure or revision by operative intervention indicated	Life-threatening consequences; symptomatic hernia with evidence of strangulation; fascial disruption with evisceration; major reconstruction flap, grafting, resection, or amputation indicated	Death
Definition: A finding of separation	of the approximated margins of a	surgical wound.	T	Г	1
Wrist fracture	Mild; non-surgical intervention indicated	Limiting instrumental ADL; operative intervention indicated	Limiting self care ADL; elective surgery indicated	-	-
Definition: A finding of traumatic	injury to the wrist joint in which the	continuity of a wrist bone is broke	en.		
Injury, poisoning and procedural complications - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

		Investigations	S		
			Grade		
Adverse Event	1	2	3	4	5
Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage	-	-
	y test result in which the partial th			possible indicator of coagulopat	hy, a prolonge
	may occur in a variety of disease				1
Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
	oratory test results that indicate a		1 ,	1	1
Alkaline phosphatase increased	1	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
	oratory test results that indicate a	·	· · · · · · · · · · · · · · · · · · ·		
Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on lab	oratory test results that indicate a	n increase in the level of aspartate	aminotransferase (AST or SGOT) in a blood specimen.	_
Blood antidiuretic hormone abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Hospitalization indicated	-	-
Definition: A finding based on lab	oratory test results that indicate a	bnormal levels of antidiuretic horm	one in the blood specimen.		
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN	-
Definition: A finding based on lab	oratory test results that indicate a	n abnormally high level of bilirubin	in the blood. Excess bilirubin is as	ssociated with jaundice.	
Blood corticotrophin decreased	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Hospitalization indicated	-	-
Definition: A finding based on lab	oratory test results that indicate a	n decrease in levels of corticotropl	nin in a blood specimen.		
Blood gonadotrophin abnormal	Asymptomatic; clinical or diagnostic observations only;	Symptomatic; medical intervention indicated; limiting	Severe symptoms; limiting self care ADL	-	-
Definition: A finding based on lab	intervention not indicated	instrumental ADL	armone in a blood anasimon		l
	oratory test results that indicate a	1	ormone in a blood specimen.		1
Blood prolactin abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	-	-	-
Definition: A finding based on lab	oratory test results that indicate a	, bnormal levels of prolactin hormor	ne in a blood specimen.	'	•
Carbon monoxide diffusing capacity decreased	3 - 5 units below LLN; for follow- up, a decrease of 3 - 5 units (ml/min/mm Hg) below the baseline value	6 - 8 units below LLN; for follow- up, an asymptomatic decrease of >5 - 8 units (ml/min/mm Hg) below the baseline value	Asymptomatic decrease of >8 units drop; >5 units drop along with the presence of pulmonary symptoms (e.g., >Grade 2 hypoxia or >Grade 2 or higher dyspnea)	-	-
Definition: A finding based on lun	g function test results that indicate	a decrease in the lung capacity	to absorb carbon monoxide.	1	,
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer	-	-
Definition: A laboratory test resul	t which indicates increased levels	of cardiac troponin I in a biologica	1	I	T
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer	-	-
Definition: A laboratory test result	t which indicates increased levels	of cardiac troponin T in a biologica	al specimen.		
CD4 lymphocytes decreased	<lln -="" 0.5="" 500="" <lln="" mm3;="" x<br="">10e9 /L</lln>	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200 - 50/mm3; <0.2 x 0.05 - 10e9 /L	<50/mm3; <0.05 x 10e9 /L	-
Definition: A finding based on lab	oratory test results that indicate a	n decrease in levels of CD4 lymph	ocytes in a blood specimen.		
Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L	-
Definition: A finding based on lab	oratory test results that indicate h	gher than normal levels of cholest	terol in a blood specimen.		
CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN	-
Definition: A finding based on lab	oratory test results that indicate a	n increase in levels of creatine pho	osphokinase in a blood specimen.		

		Investigations	•					
Grade								
Adverse Event	1	2	3	4	5			
Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	-			
Definition: A finding based on lab	oratory test results that indicate in	creased levels of creatinine in a b	iological specimen.					
Ejection fraction decreased	-	Resting ejection fraction (EF) 50 - 40%; 10 - 19% drop from baseline	Resting ejection fraction (EF) 39 - 20%; >20% drop from baseline	. ,	-			
Definition: The percentage comp contraction.	uted when the amount of blood ejo	ected during a ventricular contracti	on of the heart is compared to the	amount that was present prior to	the			
Electrocardiogram QT corrected interval prolonged		QTc 481 - 500 ms	QTc >= 501 ms on at least two separate ECGs	QTc >= 501 or >60 ms change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	-			
	dysrhythmia characterized by an a			.0.05				
Fibrinogen decreased	<1.0 - 0.75 x LLN or <25% decrease from baseline	<0.75 - 0.5 x LLN or 25 - <50% decrease from baseline	<0.5 - 0.25 x LLN or 50 - <75% decrease from baseline	<0.25 x LLN or 75% decrease from baseline or absolute value <50 mg/dL	-			
Definition: A finding based on lab	oratory test results that indicate a	n decrease in levels of fibrinogen i	n a blood specimen.					
Forced expiratory volume decreased	FEV1% (percentages of observed FEV1 and FVC related to their respective predicted values) 99 - 70% predicted	FEV1 60 - 69%	50 - 59%	<= 49%	-			
Definition: A finding based on tes	st results that indicate a relative de	crease in the fraction of the forced	l vital capacity that is exhaled in a	specific number of seconds.				
-	>ULN - 2.5 x ULN poratory test results that indicate h	-			- nma-			
	he transfer of a gamma glutamyl g T		ide to another peptide, amino acid I	s or water.				
Growth hormone abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	-	-	-			
Definition: A finding based on lab	oratory test results that indicate a	bnormal levels of growth hormone	in a biological specimen.					
Haptoglobin decreased	<lln< td=""><td>-</td><td>-</td><td>-</td><td>-</td></lln<>	-	-	-	-			
Definition: A finding based on lab	oratory test results that indicate a	n decrease in levels of haptoglobir	n in a blood specimen.					
Hemoglobin increased	Increase in >0 - 2 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN	-	-			
Definition: A finding based on lab	oratory test results that indicate in	creased levels of hemoglobin in a	biological specimen.	Г	1			
INR increased	>1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation	-	-			
Definition: A finding based on lab	oratory test results that indicate a	n increase in the ratio of the patier	nt's prothrombin time to a control s	ample in the blood.				
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN	-			
Definition: A finding based on lab	oratory test results that indicate a	n increase in the level of lipase in	a biological specimen.	Т				
Lymphocyte count decreased	<pre><lln -="" 0.8="" 10e9="" 800="" <lln="" l<="" mm3;="" pre="" x=""></lln></pre>	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	-			
	oratory test results that indicate a			1				
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	l -			
Definition: A finding based on lab Neutrophil count decreased	· ·	<1500 - 1000/mm3; <1.5 - 1.0 x	<1000 - 500/mm3; <1.0 - 0.5 x	sions or bone marrow. <500/mm3; <0.5 x 10e9 /L	-			
	10e9 /L	10e9 /L	10e9 /L		1			
Definition: A finding based on lab Pancreatic enzymes decreased	coratory test results that indicate a	Increase in stool frequency,	Sequelae of absorption	-	-			
Definition: A finding based on lab	oratory test results that indicate a	bulk, or odor; steatorrhea n decrease in levels of pancreatic	deficiency enzymes in a biological specimen	<u> </u>	l			

		Investigations			
			Grade		
Adverse Event	1	2	3	4	5
Platelet count decreased	<lln -="" -<="" 75,000="" <lln="" mm3;="" td=""><td><75,000 - 50,000/mm3; <75.0 -</td><td><50,000 - 25,000/mm3; <50.0 -</td><td><25,000/mm3; <25.0 x 10e9 /L</td><td>-</td></lln>	<75,000 - 50,000/mm3; <75.0 -	<50,000 - 25,000/mm3; <50.0 -	<25,000/mm3; <25.0 x 10e9 /L	-
	75.0 x 10e9 /L	50.0 x 10e9 /L	25.0 x 10e9 /L		
Definition: A finding based on lab	poratory test results that indicate a	decrease in number of platelets in	a blood specimen.		
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN	
Definition: A finding based on lab	oratory test results that indicate a	n increase in the levels of amylase	in a serum specimen.		
Urine output decreased	-	-	Oliguria (<80 ml in 8 hr)	Anuria (<240 ml in 24 hr)	-
Definition: A finding based on tes	st results that indicate urine produc	tion is less relative to previous ou	tput.	•	,
Vital capacity abnormal	90 - 75% of predicted value	<75 - 50% of predicted value;	<50% of predicted value;	=	-
		limiting instrumental ADL	limiting self care ADL		
Definition: A finding based on pu	lmonary function test results that in	ndicate an abnormal vital capacity	(amount of exhaled after a maxim	um inhalation) when compared to	the predicted
value.	T	T		T	1
Weight gain	5 - <10% from baseline	10 - <20% from baseline	>=20% from baseline	-	-
Definition: A finding characterize	d by an increase in overall body w	eight; for pediatrics, greater than t	he baseline growth curve.		
Weight loss	5 to <10% from baseline;	10 - <20% from baseline;	>=20% from baseline; tube	-	-
	intervention not indicated	nutritional support indicated	feeding or TPN indicated		
Definition: A finding characterize	d by a decrease in overall body we	eight; for pediatrics, less than the b	paseline growth curve.		
White blood cell decreased	<lln -="" 3.0="" 3000="" <lln="" mm3;="" td="" x<=""><td><3000 - 2000/mm3; <3.0 - 2.0 x</td><td><2000 - 1000/mm3; <2.0 - 1.0 x</td><td><1000/mm3; <1.0 x 10e9 /L</td><td>-</td></lln>	<3000 - 2000/mm3; <3.0 - 2.0 x	<2000 - 1000/mm3; <2.0 - 1.0 x	<1000/mm3; <1.0 x 10e9 /L	-
	10e9 /L	10e9 /L	10e9 /L		
Definition: A finding based on lab	poratory test results that indicate a	n decrease in number of white blo	od cells in a blood specimen.	·	
Investigations - Other, specify	Asymptomatic or mild	Moderate; minimal, local or	Severe or medically significant	Life-threatening consequences;	Death
	, , ,	noninvasive intervention	but not immediately life-	urgent intervention indicated	
	observations only; intervention	indicated; limiting age-	threatening; hospitalization or		
	not indicated	appropriate instrumental ADL	prolongation of existing		
			hospitalization indicated;		
			disabling; limiting self care ADL		

Metabolism and nutrition disorders								
Grade								
Adverse Event	1	2	3	4	5			
cidosis	pH <normal, but="">=7.3</normal,>	-	pH <7.3	Life-threatening consequences	Death			
efinition: A disorder characteri:	zed by abnormally high acidity (high	h hydrogen-ion concentration) of t	he blood and other body tissues.					
Alcohol intolerance	-	Present	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteri: omiting, indigestion and heada	zed by an increase in sensitivity to	the adverse effects of alcohol, wh	ich can include nasal congestion,	skin flushes, heart dysrhythmias,	nausea,			
Alkalosis	pH >normal, but <=7.5		pH >7.5	Life-threatening consequences	Death			
		-	1.	Life-tiffeaterining consequences	Death			
	zed by abnormally high alkalinity (lo			Life 45	D41-			
Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteria	zed by a loss of appetite.	,	,	·				
Dehydration	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated <24 hrs	IV fluids or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteria	zed by excessive loss of water from	n the body. It is usually caused by	severe diarrhea, vomiting or diaph	noresis.				
Glucose intolerance	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; dietary modification or oral agent indicated	Severe symptoms; insulin indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteriz	zed by an inability to properly meta	bolize glucose.						
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; lonized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; lonized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; lonized calcium >1.8 mmol/L; life-threatening consequences	Death			
Definition: A disorder characteria	zed by laboratory test results that ir	, ndicate an elevation in the concen	ration of calcium (corrected for all	oumin) in blood.	•			
Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life- threatening consequences	Death			
Definition: A disorder characteri: ntolerance.	zed by laboratory test results that in	ndicate an elevation in the concen	tration of blood sugar. It is usually	an indication of diabetes mellitus	or glucose			
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences	Death			
Definition: A disorder characteri: he use of diuretic drugs.	zed by laboratory test results that ir	ndicate an elevation in the concen	tration of potassium in the blood; a	associated with kidney failure or so	ometimes w			
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences	Death			
Definition: A disorder characteria	zed by laboratory test results that in	ndicate an elevation in the concen	tration of magnesium in the blood	T				
lypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death			
Definition: A disorder characteria	zed by laboratory test results that in	ndicate an elevation in the concen	tration of sodium in the blood.	Τ	T			
lypertriglyceridemia	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L; life-threatening consequences	Death			
efinition: A disorder characteriz	zed by laboratory test results that in	ndicate an elevation in the concen	tration of triglyceride concentration	n in the blood.	1			
lyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences	>10 mg/dL; >0.59 mmol/L; life- threatening consequences	Death			
efinition: A disorder characteri:	zed by laboratory test results that ir	ndicate an elevation in the concen	tration of uric acid.					
lypoalbuminemia	<lln -="" 3="" 30="" <lln="" dl;="" g="" l<="" td=""><td><3 - 2 g/dL; <30 - 20 g/L</td><td><2 g/dL; <20 g/L</td><td>Life-threatening consequences; urgent intervention indicated</td><td>Death</td></lln>	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated	Death			
efinition: A disorder characteri:	zed by laboratory test results that ir	ndicate a low concentration of albu	ımin in the blood.					

		Metabolism and nutrition	n disorders		
			Grade		
Adverse Event	1	2	3	4	5
Hypocalcemia	Corrected serum calcium of <lln -="" 2.0<br="" 8.0="" <lln="" dl;="" mg="">mmol/L; lonized calcium <lln -<br="">1.0 mmol/L</lln></lln>	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; lonized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; lonized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; Iife-threatening consequences	Death
Definition: A disorder characterize	ed by laboratory test results that ir	ndicate a low concentration of calc	ium (corrected for albumin) in the	blood.	,
Hypoglycemia	<lln -="" 3.0="" 55="" <lln="" dl;="" l<="" mg="" mmol="" td=""><td><55 - 40 mg/dL; <3.0 - 2.2 mmol/L</td><td><40 - 30 mg/dL; <2.2 - 1.7 mmol/L</td><td><30 mg/dL; <1.7 mmol/L; life- threatening consequences; seizures</td><td>Death</td></lln>	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life- threatening consequences; seizures	Death
Definition: A disorder characteriz	ed by laboratory test results that in	ndicate a low concentration of gluc	ose in the blood.		
Hypokalemia	<lln -="" 3.0="" l<="" mmol="" td=""><td><lln -="" 3.0="" l;<br="" mmol="">symptomatic; intervention indicated</lln></td><td><3.0 - 2.5 mmol/L; hospitalization indicated</td><td><2.5 mmol/L; life-threatening consequences</td><td>Death</td></lln>	<lln -="" 3.0="" l;<br="" mmol="">symptomatic; intervention indicated</lln>	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death
Definition: A disorder characteriz	ed by laboratory test results that ir	ndicate a low concentration of pota	assium in the blood.		
Hypomagnesemia	<lln -="" 0.5="" 1.2="" <lln="" dl;="" l<="" mg="" mmol="" td=""><td><1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L</td><td><0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L</td><td><0.7 mg/dL; <0.3 mmol/L; life-threatening consequences</td><td>Death</td></lln>	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; life-threatening consequences	Death
Definition: A disorder characteriz	ed by laboratory test results that in	ndicate a low concentration of mag	nesium in the blood.		
Hyponatremia	<lln -="" 130="" l<="" mmol="" td=""><td>-</td><td><130 - 120 mmol/L</td><td><120 mmol/L; life-threatening consequences</td><td>Death</td></lln>	-	<130 - 120 mmol/L	<120 mmol/L; life-threatening consequences	Death
Definition: A disorder characteriz	ed by laboratory test results that ir	ndicate a low concentration of sod	um in the blood.		
Hypophosphatemia	<lln -="" 0.8="" 2.5="" <lln="" dl;="" l<="" mg="" mmol="" td=""><td><2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L</td><td><2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L</td><td><1.0 mg/dL; <0.3 mmol/L; life- threatening consequences</td><td>Death</td></lln>	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L	<1.0 mg/dL; <0.3 mmol/L; life- threatening consequences	Death
Definition: A disorder characteriz	ed by laboratory test results that in	ndicate a low concentration of pho	sphates in the blood.		
Iron overload	-	Moderate symptoms; intervention not indicated	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by accumulation of iron in the ti	issues.			
Obesity	-	BMI 25 - 29.9 kg/m2	BMI 30 - 39.9 kg/m2	BMI >=40 kg/m2	-
Definition: A disorder characteriz	ed by having a high amount of boo	dy fat.			
Tumor lysis syndrome	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by metabolic abnormalities that	t result from a spontaneous or the	rapy-related cytolysis of tumor cell	S	
Metabolism and nutrition disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Musculoskeletal and connective tissue disorders								
	Grade 4 2 3 4							
Adverse Event	1	2	3	4	5			
Abdominal soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical	Operative debridement or other invasive intervention indicated (e.g. tissue reconstruction, flap	Life-threatening consequences; urgent intervention indicated	Death			
		medications)	or grafting)					
	1	g in the soft tissues of the abdomir						
Arthralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
	ed by a sensation of marked disco		1		1			
Arthritis	Mild pain with inflammation, erythema, or joint swelling	Moderate pain associated with signs of inflammation, erythema, or joint swelling; limiting instrumental ADL	Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self care ADL	-	-			
Definition: A disorder characteriz	ed by inflammation involving a joi			i	1			
Avascular necrosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
	ed by necrotic changes in the bon d the destruction of the bone stru		od supply. Most often affecting the	epiphysis of the long bones, the r	ecrotic			
Back pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characteriz	ed by marked discomfort sensation	n in the back region.						
Bone pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characteriz	ed by marked discomfort sensation	n in the bones.		1				
Buttock pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characteriz	ed by marked discomfort sensation	n in the buttocks.	1	_				
Chest wall pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characteriz	ed by marked discomfort sensation	n in the chest wall region.						
Exostosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	-	-			
Definition: A disorder characteriz	ed by non-neoplastic overgrowth	of bone.	1	ı	ų.			
Fibrosis deep connective tissue	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration; unable to slide or pinch skin; limiting joint or orifice movement (e.g. mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death			
	ed by fibrotic degeneration of the							
Flank pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
	1	•	the region below the ribs and abo	ove the hip.	1			
Generalized muscle weakness	Symptomatic; weakness perceived by patient but not evident on physical exam	Symptomatic; weakness evident on physical exam; weakness limiting instrumental ADL	Weakness limiting self care ADL; disabling	-	-			
Definition: A disorder characteriz	ed by a reduction in the strength	of muscles in multiple anatomic sit	es.					
Growth suppression	Reduction in growth velocity by 10 - 29% ideally measured over the period of a year	Reduction in growth velocity by 30 - 49% ideally measured over the period of a year or 0 - 49% reduction in growth from the	Reduction in growth velocity of >=50% ideally measured over the period of a year	-	-			
		baseline growth curve						

Grade								
Adverse Event	1	2	3	4				
Head soft tissue necrosis	-	Local wound care; medical	Operative debridement or other	Life-threatening consequences;	Death			
		intervention indicated (e.g.,	invasive intervention indicated	urgent intervention indicated				
		dressings or topical	(e.g., tissue reconstruction, flap					
		medications)	or grafting)					
Definition: A disorder characteriz	ed by a necrotic process occurring	in the soft tissues of the head.	1					
Joint effusion	Asymptomatic; clinical or	Symptomatic; limiting	Severe symptoms; limiting self	-	_			
	diagnostic observations only;	instrumental ADL	care ADL; elective operative					
	intervention not indicated	in or arrivation at 7 to 2	intervention indicated; disabling					
Definition: ∆ disorder characteriz	ed by excessive fluid in a joint, usu	l Ially as a result of joint inflammati	-		ı			
		>25 - 50% decrease in ROM;	>50% decrease in ROM; limiting					
Joint range of motion decreased		· ·	, ,	-	-			
	motion); decreased ROM	limiting instrumental ADL	self care ADL; disabling					
5 5 W A P A A A A A A A A A A A A A A A A A	limiting athletic activity	· · · · ·			l			
	ed by a decrease in joint flexibility							
Joint range of motion decreased	Mild restriction of rotation or	Rotation <60 degrees to right or	Ankylosed/fused over multiple	-	-			
cervical spine	flexion between 60 - 70 degrees	left; <60 degrees of flexion	segments with no C-spine					
			rotation		l			
Definition: A disorder characteriz	ed by a decrease in flexibility of a	cervical spine joint.	T		1			
Joint range of motion decreased	Stiffness; difficulty bending to	Pain with range of motion	<50% lumbar spine flexion;	-	-			
lumbar spine	the floor to pick up a very light	(ROM) in lumbar spine; requires	associated with symptoms of					
	object but able to do athletic	a reaching aid to pick up a very	ankylosis or fused over multiple					
	activity	light object from the floor	segments with no L-spine					
			flexion (e.g., unable to reach to					
			floor to pick up a very light					
			object)					
Definition: A disorder characteriz	ed by a decrease in flexibility of a l	lumbar spine joint.						
Kyphosis	Asymptomatic; clinical or	Moderate accentuation; limiting	Severe accentuation; operative	-	-			
	diagnostic observations only;	instrumental ADL	intervention indicated; limiting					
	intervention not indicated		self care ADL					
Definition: A disorder characteriz	ed by an abnormal increase in the	curvature of the thoracic portion of	of the spine.					
Lordosis	Asymptomatic; clinical or	Moderate accentuation; limiting	Severe accentuation; operative	-	_			
	diagnostic observations only;	instrumental ADL	intervention indicated; limiting					
	intervention not indicated		self care ADL					
Definition: A disorder characteriz	ed by an abnormal increase in the	curvature of the lumbar portion of	1		ı			
Muscle weakness left-sided		Symptomatic; evident on	Limiting self care ADL; disabling					
wuscie weakiless leit-sided	Symptomatic; perceived by patient but not evident on	1 * '	Limiting sell care ADL, disabiling	-	-			
	physical exam	physical exam; limiting instrumental ADL						
Definition: A diserder sharestoriz	1	l	l a hadu		ı			
	ed by a reduction in the strength o							
Muscle weakness lower limb	Symptomatic; perceived by patient but not evident on	Symptomatic; evident on	Limiting self care ADL; disabling	-	-			
MIND SOIL MEANINGS IOMEI IIIID		physical exam; limiting						
WILLSONG WEARINGSS IOWEL IIIIID	l'							
	physical exam	instrumental ADL			1			
	l'	instrumental ADL			· -			
Definition: A disorder characteriz	physical exam ed by a reduction in the strength o Symptomatic; perceived by	instrumental ADL f the lower limb muscles. Symptomatic; evident on	Limiting self care ADL; disabling	-	-			
	physical exam ed by a reduction in the strength o	instrumental ADL f the lower limb muscles. Symptomatic; evident on physical exam; limiting	Limiting self care ADL; disabling	-	-			
Definition: A disorder characteriz	physical exam ed by a reduction in the strength o Symptomatic; perceived by	instrumental ADL f the lower limb muscles. Symptomatic; evident on	Limiting self care ADL; disabling	-	-			
Definition: A disorder characteriz Muscle weakness right-sided	physical exam ed by a reduction in the strength o Symptomatic; perceived by patient but not evident on	instrumental ADL f the lower limb muscles. Symptomatic; evident on physical exam; limiting instrumental ADL		-	-			
Definition: A disorder characteriz Muscle weakness right-sided	physical exam ed by a reduction in the strength o Symptomatic; perceived by patient but not evident on physical exam	instrumental ADL f the lower limb muscles. Symptomatic; evident on physical exam; limiting instrumental ADL		-	-			
Definition: A disorder characteriz Muscle weakness right-sided Definition: A disorder characteriz	physical exam ed by a reduction in the strength of Symptomatic; perceived by patient but not evident on physical exam ed by a reduction in the strength of	instrumental ADL f the lower limb muscles. Symptomatic; evident on physical exam; limiting instrumental ADL f the muscles on the right side of	he body.	-	-			
Definition: A disorder characteriz Muscle weakness right-sided Definition: A disorder characteriz	physical exam ed by a reduction in the strength o Symptomatic; perceived by patient but not evident on physical exam ed by a reduction in the strength o Symptomatic; perceived by	instrumental ADL f the lower limb muscles. Symptomatic; evident on physical exam; limiting instrumental ADL f the muscles on the right side of the symptomatic; evident on	he body.	-	-			
Definition: A disorder characteriz Muscle weakness right-sided Definition: A disorder characteriz Muscle weakness trunk	physical exam ed by a reduction in the strength o Symptomatic; perceived by patient but not evident on physical exam ed by a reduction in the strength o Symptomatic; perceived by patient but not evident on	instrumental ADL f the lower limb muscles. Symptomatic; evident on physical exam; limiting instrumental ADL f the muscles on the right side of the muscles on the right side of the physical exam; limiting instrumental ADL	he body.	-	-			
Definition: A disorder characteriz Muscle weakness right-sided Definition: A disorder characteriz Muscle weakness trunk Definition: A disorder characteriz	physical exam ed by a reduction in the strength of Symptomatic; perceived by patient but not evident on physical exam ed by a reduction in the strength of Symptomatic; perceived by patient but not evident on physical exam ed by a reduction in the strength of the streng	instrumental ADL f the lower limb muscles. Symptomatic; evident on physical exam; limiting instrumental ADL f the muscles on the right side of the Symptomatic; evident on physical exam; limiting instrumental ADL f the trunk muscles.	he body. Limiting self care ADL; disabling	-	-			
Definition: A disorder characteriz Muscle weakness right-sided Definition: A disorder characteriz Muscle weakness trunk Definition: A disorder characteriz	physical exam ed by a reduction in the strength of Symptomatic; perceived by patient but not evident on physical exam ed by a reduction in the strength of Symptomatic; perceived by patient but not evident on physical exam ed by a reduction in the strength of Symptomatic; perceived by Symptomatic; perceived by	instrumental ADL f the lower limb muscles. Symptomatic; evident on physical exam; limiting instrumental ADL f the muscles on the right side of the muscles on the right side of the symptomatic; evident on physical exam; limiting instrumental ADL f the trunk muscles. Symptomatic; evident on	he body.	-	-			
Definition: A disorder characteriz Muscle weakness right-sided Definition: A disorder characteriz Muscle weakness trunk	physical exam ed by a reduction in the strength of Symptomatic; perceived by patient but not evident on physical exam ed by a reduction in the strength of Symptomatic; perceived by patient but not evident on physical exam ed by a reduction in the strength of the streng	instrumental ADL f the lower limb muscles. Symptomatic; evident on physical exam; limiting instrumental ADL f the muscles on the right side of the Symptomatic; evident on physical exam; limiting instrumental ADL f the trunk muscles.	he body. Limiting self care ADL; disabling	-	-			

			Grade		
Adverse Event	1	2	3	4	5
Musculoskeletal deformity	Cosmetically and functionally insignificant hypoplasia	Deformity, hypoplasia, or asymmetry able to be remediated by prosthesis (e.g., shoe insert) or covered by clothing	Significant deformity, hypoplasia, or asymmetry, unable to be remediated by prosthesis or covered by clothing; disabling	-	-
Definition: A disorder character	ized by of a malformation of the mu	sculoskeletal system.			•
Myalgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder character	ized by marked discomfort sensatio	n originating from a muscle or gro	up of muscles.		
Myositis	Mild pain	Moderate pain associated with weakness; pain limiting instrumental ADL	Pain associated with severe weakness; limiting self care ADL	-	-
Definition: A disorder character	ized by inflammation involving the s	keletal muscles.			
Neck pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder character	ized by marked discomfort sensatio	n in the neck area.	т.	T	
Neck soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder character	ized by a necrotic process occurring	in the soft tissues of the neck.		_	
Osteonecrosis of jaw	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (e.g., topical agents); limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder character	zed by a necrotic process occurring	g in the bone of the mandible.			
Osteoporosis	Radiologic evidence of osteoporosis or Bone Mineral Density (BMD) t-score -1 to -2.5 (osteopenia); no loss of height or intervention indicated	BMD t-score <-2.5; loss of height <2 cm; anti-osteoporotic therapy indicated; limiting instrumental ADL	Loss of height >=2 cm; hospitalization indicated; limiting self care ADL	-	-
Definition: A disorder charactericomposition), resulting in increa	ized by reduced bone mass, with a ased fracture incidence.	decrease in cortical thickness and	in the number and size of the trab	peculae of cancellous bone (but no	ormal chei
Pain in extremity	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder character	zed by marked discomfort sensatio	n in the upper or lower extremities	b.		
Pelvic soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death
	ized by a necrotic process occurring	1	. 45 damas a		
Scoliosis	<20 degrees; clinically undetectable	>20 - 45 degrees; visible by forward flexion; limiting instrumental ADL	>45 degrees; scapular prominence in forward flexion; operative intervention indicated; limiting self care ADL; disabling	-	-
Definition: A disorder character	ized by a malformed, lateral curvatu	ire of the spine.			
Soft tissue necrosis lower limb	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder character	zed by a necrotic process occurring	in the soft tissues of the lower ex	tremity.		
Soft tissue necrosis upper limb	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death

	Musculoskeletal and connective tissue disorders								
			Grade						
Adverse Event	1	2	3	4	5				
Superficial soft tissue fibrosis	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration; unable to slide or pinch skin; limiting joint or orifice movement (e.g., mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death				
Definition: A disorder characterize	ed by fibrotic degeneration of the s	superficial soft tissues.							
Trismus	Decreased ROM (range of motion) without impaired eating	Decreased ROM requiring small bites, soft foods or purees	Decreased ROM with inability to adequately aliment or hydrate orally	-	-				
Definition: A disorder characterize	ed by lack of ability to open the mo	outh fully due to a decrease in the	range of motion of the muscles of	mastication.					
Unequal limb length	Mild length discrepancy <2 cm	Moderate length discrepancy 2 - 5 cm; shoe lift indicated; limiting instrumental ADL	, ,	-	-				
Definition: A disorder characterize	ed by of a discrepancy between th	e lengths of the lower or upper ex	tremities.						
Musculoskeletal and connective tissue disorder - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death				

	Neoplasms benig	n, malignant and unspec	cified (incl cysts and poly	yps)				
		Grade						
Adverse Event	1	2	3	4	5			
Leukemia secondary to oncology chemotherapy	-	-	-	Present	Death			
Definition: A disorder characterize	ed by leukemia arising as a result	of the mutagenic effect of chemot	herapy agents.					
Myelodysplastic syndrome	-	-	-	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characterize	ed by insufficiently healthy hemata	poietic cell production by the bone	e marrow.					
Treatment related secondary malignancy	-	-	Non life-threatening secondary malignancy	Acute life-threatening secondary malignancy; blast crisis in leukemia	Death			
Definition: A disorder characterize	ed by development of a malignand	by most probably as a result of trea	atment for a previously existing ma	alignancy.				
Tumor pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characterize	ed by marked discomfort from a ne	eoplasm that may be pressing on	a nerve, blocking blood vessels, ir	nflamed or fractured from metastas	sis.			
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death			

Definition: A disorder characterized by Accessory nerve disorder Definition: A disorder characterized by Accustic nerve disorder NOS Accustic nerve disorder NOS Accustic nerve disorder NOS Accustic nerve disorder NOS Accustic nerve disorder characterized by Accustic nerve disorder characterized by Akathisia Definition: A disorder characterized by Amnesia Definition: A disorder characterized by Aphonia	symptomatic; clinical or agnostic observations only; tervention not indicated by involvement of the accessor agnostic observations only; tervention not indicated by involvement of the acoustic observations only; tervention not indicated by involvement of the acoustic observations or increased of a country of the acoustic of the accessor of the acce	Moderate symptoms; limiting instrumental ADL y nerve (eleventh cranial nerve). Moderate symptoms; limiting instrumental ADL nerve (eighth cranial nerve). Moderate restlessness or increased motor activity; limiting instrumental ADL		-	-
Abducens nerve disorder Asy diag inte Definition: A disorder characterized by Accessory nerve disorder Asy diag inte Definition: A disorder characterized by Acoustic nerve disorder NOS Asy diag inte Definition: A disorder characterized by Akathisia Definition: A disorder characterized by Amnesia Milo Definition: A disorder characterized by Aphonia Definition: A disorder characterized by Aphonia Definition: A disorder characterized by Aphonia Definition: A disorder characterized by Aphonia	symptomatic; clinical or agnostic observations only; tervention not indicated by involvement of the abducent agnostic observations only; tervention not indicated by involvement of the accessor agnostic observations only; tervention not indicated by involvement of the accessor agnostic observations only; tervention not indicated by involvement of the accustic observations only; tervention not indicated by involvement of the accustic or increased of the accustic observations on increased of the accustic observations or increased of the accustic observations or increased of the accustic observations or increased of the accustic observations or increased of the accustic observations or increased of the accustic observations or increased of the accustic observations or increased of the accustic observations or increased of the accustic observations or increased of the accustic observations or increased of the accustic observations or increased of the accustic observations or increased of the accustic observations or increased of the accustic observations or increased of the accustic observations or increased observations or	Moderate symptoms; limiting instrumental ADL s nerve (sixth cranial nerve). Moderate symptoms; limiting instrumental ADL y nerve (eleventh cranial nerve). Moderate symptoms; limiting instrumental ADL nerve (eighth cranial nerve). Moderate restlessness or increased motor activity; limiting instrumental ADL	Severe symptoms; limiting self care ADL Severe symptoms; limiting self care ADL Severe symptoms; limiting self care ADL Severe restlessness or increased motor activity; limiting	-	-
Definition: A disorder characterized by Accessory nerve disorder Definition: A disorder characterized by Accessory nerve disorder Definition: A disorder characterized by Accessory nerve disorder NOS Accessory nerve disorder characterized by Accessory nerve disorder characterized by Accessory nerve disorder nos Accessory nerve diso	agnostic observations only; tervention not indicated by involvement of the abducens symptomatic; clinical or agnostic observations only; tervention not indicated by involvement of the accessor symptomatic; clinical or agnostic observations only; tervention not indicated by involvement of the accustic observations only; tervention not indicated by involvement of the acoustic of lid restlessness or increased other activity.	instrumental ADL s nerve (sixth cranial nerve). Moderate symptoms; limiting instrumental ADL y nerve (eleventh cranial nerve). Moderate symptoms; limiting instrumental ADL nerve (eighth cranial nerve). Moderate restlessness or increased motor activity; limiting instrumental ADL	care ADL Severe symptoms; limiting self care ADL Severe symptoms; limiting self care ADL Severe restlessness or increased motor activity; limiting	-	-
Accessory nerve disorder Asy diag inte Definition: A disorder characterized by Acoustic nerve disorder NOS Asy diag inte Definition: A disorder characterized by Akathisia Mild Mod Definition: A disorder characterized by Amnesia Mild Definition: A disorder characterized by Aphonia Definition: A disorder characterized by Aphonia Definition: A disorder characterized by Aphonia Definition: A disorder characterized by Aphonia	symptomatic; clinical or agnostic observations only; tervention not indicated by involvement of the accessor agnostic observations only; tervention not indicated by involvement of the acoustic observations only; tervention not indicated by involvement of the acoustic observations or increased of a country of the acoustic of the accessor of the acce	Moderate symptoms; limiting instrumental ADL y nerve (eleventh cranial nerve). Moderate symptoms; limiting instrumental ADL nerve (eighth cranial nerve). Moderate restlessness or increased motor activity; limiting instrumental ADL	care ADL Severe symptoms; limiting self care ADL Severe restlessness or increased motor activity; limiting	-	-
diar interpretation: A disorder characterized by Acoustic nerve disorder NOS Asy diar interpretation: A disorder characterized by Akathisia Mild Mild Amnesia Mild Amnesia Mild Aphonia - Definition: A disorder characterized by Aphonia - Definition	agnostic observations only; tervention not indicated by involvement of the accessor symptomatic; clinical or agnostic observations only; tervention not indicated by involvement of the acoustic of ld restlessness or increased otor activity by an uncomfortable feeling of i	instrumental ADL y nerve (eleventh cranial nerve). Moderate symptoms; limiting instrumental ADL nerve (eighth cranial nerve). Moderate restlessness or increased motor activity; limiting instrumental ADL	care ADL Severe symptoms; limiting self care ADL Severe restlessness or increased motor activity; limiting	-	-
Acoustic nerve disorder NOS diaginte Definition: A disorder characterized b Akathisia Milk Molecular Milk Molecular Milk Molecular Milk Molecular Milk Molecular Milk Molecular Milk Molecular Milk Definition: A disorder characterized b Aphonia - Definition: A disorder characterized b	symptomatic; clinical or agnostic observations only; ervention not indicated by involvement of the acoustic old restlessness or increased otor activity by an uncomfortable feeling of ild; transient memory loss	Moderate symptoms; limiting instrumental ADL nerve (eighth cranial nerve). Moderate restlessness or increased motor activity; limiting instrumental ADL	Severe restlessness or increased motor activity; limiting	-	-
Definition: A disorder characterized by Akathisia Mild Mild Mild Mild Mild Mild Mild Mild	agnostic observations only; ervention not indicated by involvement of the acoustic of the acou	instrumental ADL nerve (eighth cranial nerve). Moderate restlessness or increased motor activity; limiting instrumental ADL	Severe restlessness or increased motor activity; limiting	-	-
Akathisia Milo Definition: A disorder characterized by Amnesia Milo Definition: A disorder characterized by Aphonia - Definition: A disorder characterized by	ld restlessness or increased otor activity by an uncomfortable feeling of i	Moderate restlessness or increased motor activity; limiting instrumental ADL	increased motor activity; limiting	-	
Definition: A disorder characterized by Amnesia Milo Definition: A disorder characterized by Aphonia - Definition: A disorder characterized by	otor activity by an uncomfortable feeling of i	increased motor activity; limiting instrumental ADL	increased motor activity; limiting	-	
Amnesia Mild Definition: A disorder characterized by Aphonia - Definition: A disorder characterized by Amazene and Amazene and Amazene and Amazene and Amazene and Amazene and Amazene and Amazene and Amazene and Amazene	ld; transient memory loss	inner restlessness and inability to	self care ADL		-
Definition: A disorder characterized by Aphonia - Definition: A disorder characterized by			stay still; this is a side effect of sor	me psychotropic drugs.	
Aphonia - Definition: A disorder characterized by	by systematic and extensive inc	Moderate; short term memory loss; limiting instrumental ADL	Severe; long term memory loss; limiting self care ADL	-	-
Definition: A disorder characterized by		ss of memory.	I		Τ
		-	Voicelessness; unable to speak	1	-
Arachnoiditis		-		i i	T
		Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by		•	· ·		
diag		Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; mechanical assistance indicated	-	-
Definition: A disorder characterized by	by lack of coordination of muscl	le movements resulting in the imp	airment or inability to perform volu	ntary activities.	
dia		Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by	by regional paresthesia of the b	orachial plexus, marked discomfor	t and muscle weakness, and limite	ed movement in the arm or hand.	
necrosis diag	symptomatic; clinical or agnostic observations only; ervention not indicated	Moderate symptoms; corticosteroids indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by	by a necrotic process occurring	in the brain and/or spinal cord.	1	_	
Pos hea	adache; postural care dicated	Post-craniotomy: moderate symptoms; medical intervention indicated; Post-lumbar puncture: persistent moderate symptoms; blood patch indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by	by loss of cerebrospinal fluid int	to the surrounding tissues.	1	_	
inte per edu	erfering with work/school/life erformance; specialized ducational services/devices et indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	-	-
Definition: A disorder characterized by	by a conspicuous change in coo	gnitive function.	1		
· ·	vel of concentration	Moderate impairment in attention or decreased level of concentration; limiting instrumental ADL	Severe impairment in attention or decreased level of concentration; limiting self care ADL	-	-

Nervous system disorders Grade							
Adverse Event	1	2	3	4	5		
Adverse Event	Decreased level of alertness	Sedation; slow response to	Difficult to arouse				
Depressed level of consciousness	Decreased level of alerthess	stimuli; limiting instrumental ADL	Difficult to arouse	Life-threatening consequences	Death		
Definition: A disorder characte	rized by a decrease in ability to perc	eive and respond.	'	'			
Dizziness	Mild unsteadiness or sensation	Moderate unsteadiness or	Severe unsteadiness or	-	-		
	of movement	sensation of movement; limiting instrumental ADL	sensation of movement; limiting self care ADL				
Definition: A disorder characte	rized by a disturbing sensation of lig	htheadedness, unsteadiness, gidd	liness, spinning or rocking.				
Dysarthria	Mild slurred speech	Moderate impairment of articulation or slurred speech	Severe impairment of articulation or slurred speech	-	-		
Definition: A disorder characte	rized by slow and slurred speech re	sulting from an inability to coordina	ate the muscles used in speech.				
Dysesthesia	Mild sensory alteration	Moderate sensory alteration; limiting instrumental ADL	Severe sensory alteration; limiting self care ADL	-	-		
Definition: A disorder characte	rized by distortion of sensory percep	tion, resulting in an abnormal and	unpleasant sensation.	'			
Dysgeusia	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	-	-	-		
Definition: A disorder characte	ा rized by abnormal sensual experien	ı	। an be related to a decrease in the s	sense of smell.	ı		
Dysphasia	Awareness of receptive or expressive characteristics; not	Moderate receptive or expressive characteristics; impairing ability to communicate spontaneously	Severe receptive or expressive characteristics; impairing ability	-	-		
Definition: A disorder characte	rized by impairment of verbal comm	unication skills, often resulting fron	n brain damage.	ı			
Edema cerebral	-	-	-	Life-threatening consequences; urgent intervention indicated	-		
Definition: A disorder characte	rized by swelling due to an excessiv	e accumulation of fluid in the brain	l. T	T			
Encephalopathy	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characte	rized by a pathologic process involving	ing the brain.	1	Г	1		
Extrapyramidal disorder	Mild involuntary movements	Moderate involuntary movements; limiting instrumental ADL	Severe involuntary movements or torticollis; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characte	rized by abnormal, repetitive, involu	ntary muscle movements, frenzied	speech and extreme restlessness	S.			
Facial muscle weakness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-		
Definition: A disorder characte	rized by a reduction in the strength o	of the facial muscles.	1	<u> </u>			
Facial nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-		
Definition: A disorder characte	rized by involvement of the facial ne	rve (seventh cranial nerve).					
Glossopharyngeal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characte	rized by involvement of the glossoph	naryngeal nerve (ninth cranial nerv	e).				
Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-		
Definition: A disorder characte	rized by a sensation of marked disco	omfort in various parts of the head	, not confined to the area of distrib	ution of any nerve.			
Hydrocephalus	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; intervention not indicated	Severe symptoms or neurological deficit; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characte	rized by an abnormal increase of ce	· rebrospinal fluid in the ventricles o					
Hypersomnia	Mild increased need for sleep	Moderate increased need for sleep	Severe increased need for sleep	-	-		
Definition: A disorder aborests	rized by characterized by excessive		•	•	•		

Nervous system disorders									
Grade									
Adverse Event	1	2	3	4	5				
lypoglossal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-				
Definition: A disorder characteriz	ed by involvement of the hypoglos	sal nerve (twelfth cranial nerve).		T					
ntracranial hemorrhage	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death				
Definition: A disorder characteriz	ed by bleeding from the cranium.								
schemia cerebrovascular	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	-	-	-				
Definition: A disorder characteriz damage.	red by a decrease or absence of bl	ood supply to the brain caused by	obstruction (thrombosis or embol	ism) of an artery resulting in neuro	ological				
Vth nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-				
Definition: A disorder characteriz	ed by involvement of the trochlear	nerve (fourth cranial nerve).	1	1					
Lethargy	Mild symptoms; reduced alertness and awareness	Moderate symptoms; limiting instrumental ADL	-	-	-				
Definition: A disorder characteriz	ed by a decrease in consciousnes	s characterized by mental and ph	ysical inertness.	_					
_eukoencephalopathy	Asymptomatic; small focal T2/FLAIR hyperintensities; involving periventricular white matter or <1/3 of susceptible areas of cerebrum +/- mild increase in subarachnoid space (SAS) and/or mild ventriculomegaly	Moderate symptoms; focal T2/FLAIR hyperintensities, involving periventricular white matter extending into centrum semiovale or involving 1/3 to 2/3 of susceptible areas of cerebrum +/- moderate increase in SAS and/or moderate ventriculomegaly	+/- moderate to severe increase	Life-threatening consequences; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving most of susceptible areas of cerebrum +/- moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Death				
Definition: A disorder characteriz	ed by diffuse reactive astrocytosis		i ci without inflammation	, ,	1				
Memory impairment	Mild memory impairment	Moderate memory impairment;	Severe memory impairment; limiting self care ADL	-	-				
Definition: A disorder characteriz	ed by a deterioration in memory fu	inction.	•	•					
Meningismus	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death				
Definition: A disorder characteriz	ed by neck stiffness, headache, ar	nd photophobia resulting from irrita	ation of the cerebral meninges.						
Movements involuntary	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-				
Definition: A disorder characteriz	ed by uncontrolled and purposeles	ss movements.	1	1					
⁄lyelitis	Asymptomatic; mild signs (e.g., Babinski's reflex or Lhermitte's sign)	Moderate weakness or sensory loss; limiting instrumental ADL	Severe weakness or sensory loss; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death				
Definition: A disorder characteriz	red by inflammation involving the s	pinal cord. Symptoms include wea	akness, paresthesia, sensory loss,	marked discomfort and incontiner	nce.				
leuralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-				
Definition: A disorder characteriz	ed by intense painful sensation alo	ong a nerve or group of nerves.	T	T					
lystagmus	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-				
efinition: A disorder characteriz	ted by involuntary movements of the	ne eyeballs.	I	T					
Oculomotor nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-				
efinition: A disorder characteriz	ed by involvement of the oculomot	tor nerve (third cranial nerve).							
Ifactory nerve disorder	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-				

		Nervous system dis	orders		
			Grade		
Adverse Event	1	2	3	4	5
Paresthesia	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterize are experienced in the absence of	•	ensory neurons resulting in abnorr	nal cutaneous sensations of tinglir	ng, numbness, pressure, cold, and	warmth that
Peripheral motor neuropathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; assistive device indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by inflammation or degeneratio	n of the peripheral motor nerves.			
Peripheral sensory neuropathy	Asymptomatic; loss of deep tendon reflexes or paresthesia	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by inflammation or degeneratio	n of the peripheral sensory nerves	S. T		
Phantom pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterize	ed by marked discomfort related to	o a limb or an organ that is remove	ed from or is not physically part of	the body.	
Presyncope	-	Present (e.g., near fainting)	-	-	-
Definition: A disorder characterize	ed by an episode of lightheadedne	ess and dizziness which may prece	ede an episode of syncope.	<u> </u>	
Pyramidal tract syndrome	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
	ed by dysfunction of the corticospi nd a decrease in fine motor coord		cord. Symptoms include an incre	ease in the muscle tone in the lower	r extremities,
Radiculitis	Mild symptoms	Moderate symptoms; limiting instrumental ADL; medical intervention indicated	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize connecting nerve root.	ed by inflammation involving a ner	ve root. Patients experience mark	ed discomfort radiating along a ne	rve path because of spinal pressu	re on the
Recurrent laryngeal nerve palsy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	Severe symptoms; medical intervention indicated (e.g., thyroplasty, vocal cord injection)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by paralysis of the recurrent lar	yngeal nerve.			
Reversible posterior leukoencephalopathy syndrome	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; abnormal imaging studies; limiting instrumental ADL	Severe symptoms; very abnormal imaging studies; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
		=		indings of posterior leukoencephal s an acute or subacute reversible o	
Seizure	Brief partial seizure; no loss of consciousness	Brief generalized seizure	Multiple seizures despite medical intervention	Life-threatening; prolonged repetitive seizures	Death
Definition: A disorder characterize	ed by a sudden, involuntary skelet	al muscular contractions of cerebr	al or brain stem origin.		
Sinus pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterize	ed by marked discomfort in the fac	ce, between the eyes, or upper tee	th originating from the sinuses.		
Somnolence	Mild but more than usual drowsiness or sleepiness	Moderate sedation; limiting instrumental ADL	Obtundation or stupor	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by characterized by excessive	sleepiness and drowsiness.			
Spasticity	Mild or slight increase in muscle tone	Moderate increase in muscle tone and increase in resistance through range of motion	Severe increase in muscle tone and increase in resistance through range of motion	Life-threatening; unable to move active or passive range of motion	Death
Definition: A disorder characterized disturbances.	ed by increased involuntary muscl	, ,		It results in gait, movement, and sp	peech
Stroke	Asymptomatic or mild neurologic deficit; radiographic findings only	Moderate neurologic deficit	Severe neurologic deficit	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by a sudden loss of sensory fu	nction due to an intracranial vascu	lar event.	1	
Syncope Definition: A disorder characterize	- ed by spontaneous loss of conscic	- pusness caused by insufficient blo	Fainting; orthostatic collapse od supply to the brain.	-	-

		Nervous system dis	orders		
			Grade		
Adverse Event	1	2	3	4	5
Transient ischemic attacks	Mild neurologic deficit with or without imaging confirmation	Moderate neurologic deficit with or without imaging confirmation	-	-	-
Definition: A disorder characteriz	ed by a brief attack (less than 24 h	nours) of cerebral dysfunction of va	ascular origin, with no persistent n	eurological deficit.	
Tremor	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by the uncontrolled shaking mo	vement of the whole body or indiv	ridual parts.		
Trigeminal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by involvement of the trigemina	l nerve (fifth cranial nerve).			
Vagus nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by involvement of the vagus ne	rve (tenth cranial nerve).	•		
Vasovagal reaction	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz increase in the stimulation of the	ed by a sudden drop of the blood progressing vagus nerve.	oressure, bradycardia, and periph	eral vasodilation that may lead to	loss of consciousness. It results fr	om an
Nervous system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Pregna	ancy, puerperium and pe	rinatal conditions				
Grade						
1	2	3	4	5		
-	•	-	-	Fetal loss at any gestational age		
•	product of conception to show evi	dence of respiration, heartbeat, or	definite movement of a voluntary	muscle after		
t possibility of resuscitation.						
-	<10% percentile of weight for gestational age	<5% percentile of weight for gestational age	<1% percentile of weight for gestational age	-		
ed by inhibition of fetal growth resu	ulting in the inability of the fetus to	achieve its potential weight.				
,	•	Delivery of a liveborn infant at 24 to 28 weeks gestation	Delivery of a liveborn infant at 24 weeks of gestation or less	-		
ed by delivery of a viable infant be	fore the normal end of gestation.	Typically, viability is achievable be	tween the twentieth and thirty-sev	enth week of		
-	-	Unintended pregnancy	-	-		
ed by an unexpected pregnancy a	t the time of conception.	•	•	'		
		Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated;	Life-threatening consequences; urgent intervention indicated	Death		
	ted by death in utero; failure of the t possibility of resuscitation. - ted by inhibition of fetal growth resurce downward of a liveborn infant at >34 to 37 weeks gestation and by delivery of a viable infant be ted by an unexpected pregnancy at Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention	to by death in utero; failure of the product of conception to show evit to possibility of resuscitation. - <10% percentile of weight for gestational age ed by inhibition of fetal growth resulting in the inability of the fetus to Delivery of a liveborn infant at >34 to 37 weeks gestation Delivery of a liveborn infant at >28 to 34 weeks gestation ed by delivery of a viable infant before the normal end of gestation. - -	The dead by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or to possibility of resuscitation. -	The dead by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary to possibility of resuscitation. - <10% percentile of weight for gestational age <5% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for gestational age <1% percentile of weight for		

		Psychiatric disor	ders					
Grade								
Adverse Event	1	2	3	4	5			
Agitation	Mild mood alteration	Moderate mood alteration	not indicated	Life-threatening consequences; urgent intervention indicated	Death			
	erized by a state of restlessness asso		Irritability and tension.		ı			
Anorgasmia	Inability to achieve orgasm not adversely affecting relationship	Inability to achieve orgasm adversely affecting relationship	-	-	-			
Definition: A disorder characte	erized by an inability to achieve orgas			1				
Anxiety	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization not indicated	Life-threatening; hospitalization indicated	Death			
Definition: A disorder characte stimulus.	erized by apprehension of danger and	d dread accompanied by restlessn	ess, tension, tachycardia, and dys	pnea unattached to a clearly iden	tifiable			
Confusion	Mild disorientation	Moderate disorientation; limiting instrumental ADL	Severe disorientation; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characte	erized by a lack of clear and orderly the	nought and behavior.	1	1	1			
Delayed orgasm	Delay in achieving orgasm not adversely affecting relationship	Delay in achieving orgasm adversely affecting relationship	-	-	-			
	erized by sexual dysfunction characte		1.		1			
Delirium	Mild acute confusional state	Moderate and acute confusional state; limiting instrumental ADL	Severe and acute confusional state; limiting self care ADL; hospitalization indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death			
Definition: A disorder characte reversible condition.	erized by the acute and sudden devel	opment of confusion, illusions, mo	ovement changes, inattentiveness,	agitation, and hallucinations. Usu	ıally, it is a			
		Moderate delucional symptoms	Sovere delucional aymntoma:	Life threatening consequences	Death			
Delusions	-	Moderate delusional symptoms	Severe delusional symptoms; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death			
Definition: A disorder characte	erized by false personal beliefs held o	ontrary to reality, despite contradi	ctory evidence and common sens	e.				
Depression	Mild depressive symptoms	Moderate depressive symptoms; limiting instrumental ADL	Severe depressive symptoms; limiting self care ADL; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death			
Definition: A disorder characte	erized by melancholic feelings of grief	or unhappiness.						
Euphoria	Mild mood elevation	Moderate mood elevation	Severe mood elevation (e.g., hypomania)	-	-			
Definition: A disorder characte	erized by an exaggerated feeling of w	ell-being which is disproportionate	to events and stimuli.					
Hallucinations	Mild hallucinations (e.g., perceptual distortions)	Moderate hallucinations	Severe hallucinations; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death			
Definition: A disorder characte	erized by a false sensory perception i	n the absence of an external stime	ulus.					
Insomnia	Mild difficulty falling asleep, staying asleep or waking up early	Moderate difficulty falling asleep, staying asleep or waking up early	Severe difficulty in falling asleep, staying asleep or waking up early	-	-			
Definition: A disorder characte	erized by difficulty in falling asleep and	d/or remaining asleep.						
Libido decreased	Decrease in sexual interest not adversely affecting relationship	Decrease in sexual interest adversely affecting relationship	-	-	-			
Definition: A disorder characte	erized by a decrease in sexual desire							
Libido increased	Mild increase in sexual interest not adversely affecting relationship	Moderate increase in sexual interest adversely affecting relationship	Severe increase in sexual interest leading to dangerous behavior	-	-			
Definition: A disorder characte	erized by an increase in sexual desire	· ·	•	•	•			
Mania	Mild manic symptoms (e.g., elevated mood, rapid thoughts, rapid speech, decreased need for sleep)	Moderate manic symptoms (e.g., relationship and work difficulties; poor hygiene)	Severe manic symptoms (e.g., hypomania; major sexual or financial indiscretions); hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death			
Definition: A disorder characte	erized by excitement of psychotic prop	portions manifested by mental and	d physical hyperactivity, disorganiz	ation of behavior and elevation of	mood.			
Personality change	Mild personality change	Moderate personality change	Severe personality change; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death			

		Psychiatric disord	ders		
			Grade		
Adverse Event	1	2	3	4	5
Definition: A disorder characterize	ed by a conspicuous change in a p	person's behavior and thinking.			
Psychosis	Mild psychotic symptoms	Moderate psychotic symptoms (e.g., disorganized speech; impaired reality testing)	Severe psychotic symptoms (e.g., paranoid; extreme disorganization); hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterize tumor.	ed by personality change, impaired	d functioning, and loss of touch wi	th reality. It may be a manifestatio	n of schizophrenia, bipolar disorde	er or brain
Restlessness	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterize	ed by an inability to rest, relax or b	e still.			
Suicidal ideation	Increased thoughts of death but no wish to kill oneself	Suicidal ideation with no specific plan or intent	Specific plan to commit suicide without serious intent to die which may not require hospitalization	Specific plan to commit suicide with serious intent to die which requires hospitalization	-
Definition: A disorder characterize	ed by thoughts of taking one's owr	n life.			
Suicide attempt	-	-	Suicide attempt or gesture without intent to die which may not require hospitalization	Suicide attempt with intent to die which requires hospitalization	Death
Definition: A disorder characterize	ed by self-inflicted harm in an atter	mpt to end one's own life.			
Psychiatric disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; disabling; limiting self care ADL	Life-threatening consequences; hospitalization or urgent intervention indicated	Death

Renal and urinary disorders								
Grade								
Adverse Event	1	2	3	4	5			
Acute kidney injury Definition: A disorder character	Creatinine level increase of >0.3 mg/dL; creatinine 1.5 - 2.0 x above baseline ized by the acute loss of renal functions.	baseline	Creatinine >3 x baseline or >4.0 mg/dL; hospitalization indicated	Life-threatening consequences; dialysis indicated	Death			
causes (ureteral or bladder out		,		,,,				
Bladder perforation	-	Extraperitoneal perforation, indwelling catheter indicated	Intraperitoneal perforation; elective radiologic, endoscopic or operative intervention indicated	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death			
Definition: A disorder character	ized by a rupture in the bladder wall		1	<u> </u>	,			
Bladder spasm	Intervention not indicated	Antispasmodics indicated	Hospitalization indicated	-	-			
Definition: A disorder character	ized by a sudden and involuntary co	ontraction of the bladder wall.						
Chronic kidney disease	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <lln -="" 60<br="">ml/min/1.73 m2 or proteinuria 2+ present; urine protein/creatinine >0.5</lln>	eGFR or CrCl 59 - 30 ml/min/1.73 m2	eGFR or CrCl 29 - 15 ml/min/1.73 m2	eGFR or CrCl <15 ml/min/1.73 m2; dialysis or renal transplant indicated	Death			
Definition: A disorder character	ized by gradual and usually perman	ent loss of kidney function resulting	ng in renal failure.	-				
Cystitis noninfective	Microscopic hematuria; minimal increase in frequency, urgency, dysuria, or nocturia; new onset of incontinence	Moderate hematuria; moderate increase in frequency, urgency, dysuria, nocturia or incontinence; urinary catheter placement or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death			
Definition: A disorder character	ized by inflammation of the bladder	, which is not caused by an infectio	n of the urinary tract.	•	•			
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated; limiting self care ADL	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death			
Definition: A disorder character	ized by laboratory test results that ir	ndicate blood in the urine.						
Hemoglobinuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-			
Definition: A disorder character	ized by laboratory test results that in	ndicate the presence of free hemo	globin in the urine.					
Proteinuria	1+ proteinuria; urinary protein <1.0 g/24 hrs	Adults: 2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Pediatric: urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Adults: urinary protein >=3.5 g/24 hrs; Pediatric: urine P/C >1.9	-	-			
Definition: A disorder character	ized by laboratory test results that in	ndicate the presence of excessive	protein in the urine. It is predomin	antly albumin, but also globulin.				
Renal calculi	Asymptomatic or mild symptoms; occasional use of nonprescription analgesics indicated	Symptomatic; oral antiemetics indicated; around the clock nonprescription analgesics or any oral narcotic analgesics indicated	Hospitalization indicated; IV intervention (e.g., analgesics, antiemetics); elective endoscopic or radiologic intervention indicated	Life-threatening consequences; urgent radiologic, endoscopic or operative intervention indicated	Death			
Definition: A disorder character	ized by the formation of crystals in the	he pelvis of the kidney.						
Renal colic	Mild pain not interfering with activity; nonprescription medication indicated	Moderate pain; limiting instrumental ADL; prescription medication indicated	Hospitalization indicated; limiting self care ADL	-	-			

		Renal and urinary di	sorders		
			Grade		
Adverse Event	1	2	3	4	5
Renal hemorrhage	Mild symptoms; intervention not indicated	Analgesics and hematocrit monitoring indicated	Transfusion, radiation, or hospitalization indicated; elective radiologic, endoscopic or operative intervention indicated	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characteriz	ed by bleeding from the kidney.				
Urinary fistula	-	Noninvasive intervention indicated; urinary or suprapubic catheter placement indicated	Limiting self care ADL; elective radiologic, endoscopic or operative intervention indicated; permanent urinary diversion indicated	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characteriz	ed by an abnormal communication	between any part of the urinary s	system and another organ or anato	omic site.	
Urinary frequency	Present	Limiting instrumental ADL; medical management indicated	-	-	-
Definition: A disorder characteriz	ed by urination at short intervals.			T	1
Urinary incontinence	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous; pads indicated; limiting instrumental ADL	Intervention indicated (e.g., clamp, collagen injections); operative intervention indicated; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by inability to control the flow o	f urine from the bladder.			
Urinary retention	Urinary, suprapubic or intermittent catheter placement not indicated; able to void with some residual	Placement of urinary, suprapubic or intermittent catheter placement indicated; medication indicated	Elective operative or radiologic intervention indicated; substantial loss of affected kidney function or mass	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
Definition: A disorder characteriz	ed by accumulation of urine within	the bladder because of the inabil	ity to urinate.		
Urinary tract obstruction	Asymptomatic; clinical or diagnostic observations only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; urethral dilation, urinary or suprapubic catheter indicated	Symptomatic and altered organ function (e.g., hydronephrosis, or renal dysfunction); elective radiologic, endoscopic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by blockage of the normal flow	of contents of the urinary tract.			
Urinary tract pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by a sensation of marked disco	omfort in the urinary tract.			
Urinary urgency	Present	Limiting instrumental ADL; medical management indicated	-	-	-
Definition: A disorder characteriz	ed by a sudden compelling urge to	urinate.			
Urine discoloration	Present	-	-	-	-
Definition: A disorder characteriz	ed by a change in the color of the	urine.			•
Renal and urinary disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate, local or noninvasive intervention indicated; limiting instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

	Rep	productive system and b	reast disorders		
			Grade		
Adverse Event	1	2	3	4	5
Azoospermia	-	-	Absence of sperm in ejaculate	-	-
Definition: A disorder characte	erized by laboratory test results that ir	ndicate complete absence of speri	matozoa in the semen.		•
Breast atrophy	Minimal asymmetry; minimal	Moderate asymmetry; moderate	Asymmetry >1/3 of breast	-	-
	atrophy	atrophy	volume; severe atrophy		
Definition: A disorder characte	erized by underdevelopment of the br	east.	'	'	•
Breast pain	Mild pain	Moderate pain; limiting	Severe pain; limiting self care	-	_
,		instrumental ADL	ADL		
Definition: A disorder characte	erized by marked discomfort sensation	n in the breast region.	'	'	•
Dysmenorrhea	Mild symptoms; intervention not		Severe symptoms; limiting self	_	_
-,	indicated	instrumental ADL	care ADL		
Definition: A disorder characte	erized by abnormally painful abdomin	al cramps during menses.	!	!	'
Dyspareunia	Mild discomfort or pain	Moderate discomfort or pain	Severe discomfort or pain		
3y3parcuma	associated with vaginal	associated with vaginal	associated with vaginal		
	penetration; discomfort relieved	penetration; discomfort or pain	penetration; discomfort or pain		
	with use of vaginal lubricants or	partially relieved with use of	unrelieved by vaginal lubricants		
	estrogen	vaginal lubricants or estrogen	or estrogen		
Definition: A disorder characte	erized by painful or difficult coitus.				_
Ejaculation disorder	Diminished ejaculation	Anejaculation or retrograde	-	-	-
		ejaculation			
Definition: A disorder characte	erized by problems related to ejaculat	, ion. This category includes prema	ture, delayed, retrograde and pair	ful ejaculation.	•
Erectile dysfunction	Decrease in erectile function	Decrease in erectile function	Decrease in erectile function	-	_
,	(frequency or rigidity of	(frequency/rigidity of erections),	(frequency/rigidity of erections)		
	erections) but intervention not	erectile intervention indicated,	but erectile intervention not		
	indicated (e.g., medication or	(e.g., medication or mechanical	helpful (e.g., medication or		
	use of mechanical device,	devices such as penile pump)	mechanical devices such as		
	penile pump)		penile pump); placement of a		
			permanent penile prosthesis		
			indicated (not previously present)		
Definition: A disorder character	rized by the persistent or recurrent in	 		I	1
	erized by the persistent or recurrent in				
Fallopian tube obstruction	Diagnostic observations only;	Mild symptoms; elective	Severe symptoms; elective	=	-
	intervention not indicated	intervention indicated	operative intervention indicated		l
Definition: A disorder characte	erized by blockage of the normal flow	of the contents in the fallopian tub	oe.		
Fallopian tube stenosis	Asymptomatic clinical or	Symptomatic and intervention	Severe symptoms; elective	Life-threatening consequences;	Death
	diagnostic observations only;	not indicated	operative intervention indicated	urgent operative intervention	
	intervention not indicated			indicated (e.g., organ resection)	I
	erized by a narrowing of the fallopian				1
Female genital tract fistula	Asymptomatic clinical or	Symptomatic and intervention	Severe symptoms; elective	Life-threatening consequences;	Death
	diagnostic observations only;	not indicated	operative intervention indicated	urgent intervention indicated	
	intervention not indicated				I
Definition: A disorder characte	erized by an abnormal communication	n between a female reproductive s	system organ and another organ o	r anatomic site.	
Feminization acquired	Mild symptoms; intervention not	1	-	-	-
	indicated	intervention indicated			
Definition: A disorder characte	erized by the development of seconda	ary female sex characteristics in m	nales due to extrinsic factors.	1	
Genital edema	Mild swelling or obscuration of	Readily apparent obscuration of	Lymphorrhea; gross deviation	-	-
	anatomic architecture on close	anatomic architecture;	from normal anatomic contour;		
	inspection	obliteration of skin folds; readily	limiting self care ADL		
		apparent deviation from normal			
Definition, A dis	primad by availing due to an arm	anatomic contour		I	I
	erized by swelling due to an excessive				
Gynecomastia	Asymptomatic breast	Symptomatic (e.g., pain or	Severe symptoms; elective	-	-
	enlargement	psychosocial impact)	operative intervention indicated		I
Definition: A disorder characte	erized by excessive development of the	ne breasts in males.	1	1	_
Hematosalpinx	Minimal bleeding identified on	Moderate bleeding; medical	Severe bleeding; transfusion	Life-threatening consequences;	Death
	imaging study or laparoscopy;	intervention indicated	indicated; radiologic or	urgent operative intervention	
	intervention not indicated		endoscopic intervention	indicated	
	1	l .	indicated	1	1

	Rep	productive system and bi	east disorders					
	Grade							
Adverse Event	1	2	3	4	5			
Definition: A disorder characteri	ized by the presence of blood in a fa	allopian tube.						
rregular menstruation	Intermittent menses with skipped menses for no more than 1 to 3 months	Intermittent menses with skipped menses for more than 4 to 6 months	Persistent amenorrhea for more than 6 months	-	-			
Definition: A disorder characteri	ized by irregular cycle or duration of	menses.	Γ	Γ	1			
actation disorder	Mild changes in lactation, not significantly affecting production or expression of breast milk	Changes in lactation, significantly affecting breast production or expression of breast milk	-	-	-			
Definition: A disorder characteri	ized by disturbances of milk secretion	on. It is not necessarily related to p	pregnancy that is observed in fema	ales and can be observed in males	S.			
Menorrhagia	Mild; iron supplements indicated	Moderate symptoms; medical intervention indicated (e.g., hormones)	Severe; transfusion indicated; surgical intervention indicated (e.g., hysterectomy)	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteri	ized by abnormally heavy vaginal bl	eeding during menses.						
Nipple deformity	Asymptomatic; asymmetry with slight retraction and/or thickening of the nipple areolar complex	Symptomatic; asymmetry of nipple areolar complex with moderate retraction and/or thickening of the nipple areolar complex	-	-	-			
Definition: A disorder characteri	zed by a malformation of the nipple	•						
Oligospermia	Sperm concentration >48 million/mL or motility >68%	Sperm concentration 13 - 48 million/mL or motility 32 - 68%	Sperm concentration <13 million/mL or motility <32%	-	-			
Definition: A disorder characteri	ized by a decrease in the number of	spermatozoa in the semen.						
Ovarian hemorrhage	Minimal bleeding identified on imaging study or laproscopy; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characteri	ized by bleeding from the ovary.	1	•	'				
Ovarian rupture	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteri	ized by tearing or disruption of the c	varian tissue.	, .		'			
Ovulation pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characteri ovarian follicle.	ized by marked discomfort sensatio	n in one side of the abdomen betw	veen menstrual cycles, around the	time of the discharge of the ovum	from the			
Pelvic floor muscle weakness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic, not interfering with bladder, bowel, or vaginal function; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteri	zed by a reduction in the strength o	f the muscles of the pelvic floor.						
elvic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characteri	ized by marked discomfort sensatio	n in the pelvis.	I	I	1			
Penile pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
	ized by marked discomfort sensatio				1			
erineal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characteri	ized by a sensation of marked disco	mfort in the area between the ger	T	Т				
Premature menopause	-	-	Present	-	-			
Definition: A disorder characteri	zed by ovarian failure before the ag	e of 40. Symptoms include hot fla	shes, night sweats, mood swings	and a decrease in sex drive.				
Prostatic hemorrhage	Minimal bleeding identified on imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			

	Rep	productive system and be	reast disorders		
			Grade		
Adverse Event	1	2	3	4	5
Definition: A disorder characteriz	red by bleeding from the prostate of	pland.	1		
Prostatic obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characteriz stream, and incomplete emptyin	zed by compression of the urethra g of the bladder).	secondary to enlargement of the p	prostate gland. This results in voidi	ng difficulties (straining to void, sl	ow urine
Prostatic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by a sensation of marked disco	omfort in the prostate gland.			
Scrotal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by marked discomfort sensatio	n in the scrotal area.			
Spermatic cord hemorrhage	Minimal bleeding identified on imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteriz	ed by bleeding from the spermatic	cord.			
Spermatic cord obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characteriz	ed by blockage of the normal flow	of the contents of the spermatic c	ord.		
Festicular disorder	Asymptomatic; clinical or diagnostic observations only;	Symptomatic but not interfering with urination or sexual	Severe symptoms; interfering with urination or sexual function;	Life-threatening consequences; urgent intervention indicated	Death
	intervention not indicated	activities; intervention not indicated; limiting instrumental ADL	limiting self care ADL; intervention indicated		
Definition: A disorder characteriz	ed by involvement of the testis.	ı	!		'
Testicular hemorrhage	Minimal bleeding identified on imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteriz	red by bleeding from the testis.	1	1		
「esticular pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by a sensation of marked disco	omfort in the testis.			
Jterine fistula	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by an abnormal communication	n between the uterus and another	organ or anatomic site.		'
Jterine hemorrhage	Minimal bleeding identified on imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteriz	red by bleeding from the uterus.				
Iterine obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characteriz	zed by blockage of the uterine outle	et.			
Iterine pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	red by a sensation of marked disco	omfort in the uterus.			
/aginal discharge	Mild vaginal discharge (greater than baseline for patient)	Moderate to heavy vaginal discharge; use of perineal pad or tampon indicated	-	-	-
Definition: A disorder characteriz	ed by vaginal secretions. Mucus p		discharged from the vagina natura	lly, especially during the childbea	ring years.
/aginal dryness	Mild vaginal dryness not interfering with sexual function	Moderate vaginal dryness interfering with sexual function	Severe vaginal dryness resulting in dyspareunia or severe discomfort	-	-
Definition: A disorder characteriz	l red by an uncomfortable feeling of	or causing frequent discomfort itching and burning in the vagina.	Joseph discombit	I	1

	Rep	productive system and b	reast disorders		
			Grade		
Adverse Event	1	2	3	4	5
Vaginal fistula	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by an abnormal communication	between the vagina and another	organ or anatomic site.		
Vaginal hemorrhage	Minimal bleeding identified on clinical exam or imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterize	ed by bleeding from the vagina.				
Vaginal inflammation	Mild discomfort or pain, edema, or redness	Moderate discomfort or pain, edema, or redness; limiting instrumental ADL	Severe discomfort or pain, edema, or redness; limiting self care ADL; small areas of mucosal ulceration	Widespread areas of mucosal ulceration; life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by inflammation involving the v	agina. Symptoms may include red	lness, edema, marked discomfort	and an increase in vaginal dischar	ge.
Vaginal obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterize	ed by blockage of vaginal canal.		1	1	
Vaginal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterize	ed by a sensation of marked disco	mfort in the vagina.			
Vaginal perforation	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by a rupture in the vaginal wall.				•
Vaginal stricture	Asymptomatic; mild vaginal shortening or narrowing	Vaginal narrowing and/or shortening not interfering with physical examination	Vaginal narrowing and/or shortening interfering with the use of tampons, sexual activity or physical examination	-	Death
Definition: A disorder characterize	ed by a narrowing of the vaginal ca	anal.			
Vaginismus	Mild discomfort or pain associated with vaginal spasm/tightening; no impact upon sexual function or physical examination	Moderate discomfort or pain associated with vaginal spasm/tightening; disruption in sexual function and physical examination	Severe discomfort or pain associated with vaginal spasm/tightening; unable to tolerate vaginal penetration or physical examination	-	-
Definition: A disorder characterize intercourse.	ed by involuntary spasms of the pe	elvic floor muscles, resulting in pa	thologic tightness of the vaginal w	all during penetration such as duri	ng sexual
Reproductive system and breast disorders - Other, specify		Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

	Respi	ratory, thoracic and med	iastinal disorders					
	Grade							
Adverse Event	1	2	3	4	5			
Adult respiratory distress syndrome	-	-	Present with radiologic findings; intubation not indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death			
Definition: A disorder characteri surgery.	zed by progressive and life-threater	ning pulmonary distress in the abs	ence of an underlying pulmonary	condition, usually following major t	rauma or			
Allergic rhinitis	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-			
	zed by an inflammation of the nasa s of the sinuses, eyes, middle ear, a	•	•	•	ay also			
Apnea	-	-	Present; medical intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death			
Definition: A disorder characteri	zed by cessation of breathing.	I	1	T				
Aspiration	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Altered eating habits; coughing or choking episodes after eating or swallowing; medical intervention indicated (e.g., suction or oxygen)	Dyspnea and pneumonia symptoms (e.g., aspiration pneumonia); hospitalization indicated; unable to aliment orally	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death			
Definition: A disorder characteri	zed by inhalation of solids or liquids	s into the lungs.	1	<u> </u>				
Atelectasis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., dyspnea, cough); medical intervention indicated (e.g., chest physiotherapy, suctioning); bronchoscopic suctioning	Oxygen indicated; hospitalization or elective operative intervention indicated (e.g., stent, laser)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death			
Definition: A disorder characteri	zed by the collapse of part or the e	ntire lung.		T	1			
Bronchial fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical management indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death			
Definition: A disorder characteri	zed by an abnormal communication	between the bronchus and anoth	ner organ or anatomic site.	·				
Bronchial obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., mild wheezing); endoscopic evaluation indicated; radiographic evidence of atelectasis/lobar collapse; medical management indicated (e.g., steroids, bronchodilators)	Shortness of breath with stridor; endoscopic intervention indicated (e.g., laser, stent placement)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death			
Definition: A disorder characteri	zed by blockage of a bronchus pas	sage, most often by bronchial sec	retions and exudates.					
Bronchial stricture	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., rhonchi or wheezing) but without respiratory distress; medical intervention indicated (e.g., steroids, bronchodilators)	Shortness of breath with stridor; endoscopic intervention indicated (e.g., laser, stent placement)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death			
	zed by a narrowing of the bronchial			leg at the second	.			
Bronchopleural fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death			
Definition: A disorder characteri	zed by an abnormal communication	between a bronchus and the plei	ural cavity.	I				
Bronchopulmonary hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g.,	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention	Death			

	1100p	ratory, thoracic and med			
			Grade	1	_
Adverse Event	1	2	3	4	5
Bronchospasm	Mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Limiting self care ADL; oxygen saturation decreased	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder charact	terized by a sudden contraction of the	smooth muscles of the bronchial	wall.	1	1
Chylothorax	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thoracentesis or tube drainage indicated	Severe symptoms; elective operative intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder charact	terized by milky pleural effusion (abnor	rmal collection of fluid) resulting fr	om accumulation of lymph fluid in	the pleural cavity.	
Cough	Mild symptoms; nonprescription intervention indicated	Moderate symptoms, medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder charact by a distinctive sound.	terized by sudden, often repetitive, spa	asmodic contraction of the thoraci	c cavity, resulting in violent release	e of air from the lungs and usually a	accompar
Dyspnea	Shortness of breath with moderate exertion	Shortness of breath with minimal exertion; limiting instrumental ADL	Shortness of breath at rest; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder charact	terized by an uncomfortable sensation	of difficulty breathing.			
Epistaxis	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated (e.g., nasal packing, cauterization; topical vasoconstrictors)	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder charact	terized by bleeding from the nose.				
Hiccups	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe symptoms; interfering with sleep; limiting self care ADL	-	-
Definition: A disorder charact	terized by repeated gulp sounds that re	esult from an involuntary opening	and closing of the glottis. This is a	ttributed to a spasm of the diaphra	igm.
Hoarseness	Mild or intermittent voice change; fully understandable; self-resolves	Moderate or persistent voice changes; may require occasional repetition but understandable on telephone; medical evaluation indicated	Severe voice changes including predominantly whispered speech	-	-
Definition: A disorder charact	erized by harsh and raspy voice arisin	g from or spreading to the larynx.			
Hypoxia	erized by a decrease in the level of ox	Decreased oxygen saturation with exercise (e.g., pulse oximeter <88%); intermittent supplemental oxygen	Decreased oxygen saturation at rest (e.g., pulse oximeter <88% or PaO2 <=55 mm Hg)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Laryngeal edema	Asymptomatic; clinical or	Symptomatic; medical	Stridor; respiratory distress;	Life-threatening airway	Death
earyngour odollid	diagnostic observations only; intervention not indicated	intervention indicated (e.g., dexamethasone, epinephrine, antihistamines)	hospitalization indicated	compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Boun
	erized by swelling due to an excessive			Ī	I_
Laryngeal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical management indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention indicated (e.g., thoracoplasty, chronic open drainage or multiple thoracotomies)	Death
Definition: A disorder charact	erized by an abnormal communication	between the larynx and another	organ or anatomic site.		
Laryngeal hemorrhage	Mild cough or trace hemoptysis; laryngoscopic findings	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A diserder aborest	erized by bleeding from the larynx.				
Delinition. A disorder charact					

Respiratory, thoracic and mediastinal disorders							
Grade							
Adverse Event	1	2	3	4	5		
Laryngeal mucositis	Endoscopic findings only; mild discomfort with normal intake	Moderate discomfort; altered oral intake	Severe pain; severely altered eating/swallowing; medical intervention indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death		
Definition: A disorder characteri	zed by an inflammation involving th	e mucous membrane of the laryn	(.	İ			
Laryngeal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids); limiting instrumental ADL	Limiting self care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteri	zed by blockage of the laryngeal ai	rway.					
Laryngeal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Limiting self care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening consequences; urgent intervention indicated	Death		
	zed by a narrowing of the laryngea		T		I		
Laryngopharyngeal dysesthesia	a Mild symptoms; no anxiety; intervention not indicated	Moderate symptoms; mild anxiety, but no dyspnea; short duration of observation and or anxiolytic indicated; limiting instrumental ADL	Severe symptoms; dyspnea and swallowing difficulty; limiting self care ADL	Life-threatening consequences	Death		
Definition: A disorder characteri	zed by an uncomfortable persistent	sensation in the area of the laryn	gopharynx.				
Laryngospasm	-	Transient episode; intervention not indicated	Recurrent episodes; noninvasive intervention indicated (e.g., breathing technique, pressure point massage)	Persistent or severe episodes associated with syncope; urgent intervention indicated (e.g., fiberoptic laryngoscopy, intubation, botox injection)	Death		
Definition: A disorder characteri	zed by paroxysmal spasmodic mus	cular contraction of the vocal cord			'		
Mediastinal hemorrhage	Radiologic evidence only; minimal symptoms; intervention not indicated	Moderate symptoms; medical	Transfusion, radiologic, endoscopic, or elective operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteri	zed by bleeding from the mediastin	um.	1 '	l	1		
Nasal congestion	Mild symptoms; intervention not indicated		Associated with bloody nasal discharge or epistaxis	-	-		
	zed by obstruction of the nasal pas	1			ı		
Pharyngeal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteri	zed by an abnormal communication	between the pharynx and another	er organ or anatomic site.	<u> </u>			
Pharyngeal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death		
Definition: A disorder characteri	zed by bleeding from the pharynx.	T			1		
Pharyngeal mucositis	Endoscopic findings only; minimal symptoms with normal oral intake; mild pain but analgesics not indicated	Moderate pain and analgesics indicated; altered oral intake; limiting instrumental ADL	Severe pain; unable to adequately aliment or hydrate orally; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteri	zed by an inflammation involving th	e mucous membrane of the phary	nx.				
Pharyngeal necrosis	-	-	Inability to aliment adequately by GI tract; tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		

	Respi	ratory, thoracic and med	iastinal disorders		
			Grade		,
Adverse Event	1	2	3	4	5
Definition: A disorder characteriz	red by a necrotic process occurring	in the pharynx.	·	1	1
Pharyngeal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids); limiting instrumental ADL	Limiting self care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characteriz	red by a narrowing of the pharynge	al airway.	'	'	
Pharyngolaryngeal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by marked discomfort sensation	n in the pharyngolaryngeal region.	·	i .	1
Pleural effusion	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; intervention indicated (e.g., diuretics or limited therapeutic thoracentesis)	Symptomatic with respiratory distress and hypoxia; surgical intervention including chest tube or pleurodesis indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characteriz	red by an increase in amounts of flo	uid within the pleural cavity. Symp	toms include shortness of breath,	cough and marked chest discomfo	ort.
Pleural hemorrhage	Asymptomatic; mild hemorrhage confirmed by thoracentesis	Symptomatic or associated with pneumothorax; chest tube drainage indicated	>1000 ml of blood evacuated; persistent bleeding (150-200 ml/hr for 2 - 4 hr); persistent transfusion indicated; elective operative intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characteriz	ed by bleeding from the pleural ca	vity.			
Pleuritic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
	red by marked discomfort sensation	n in the pleura. I	Τ		1
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
	red by inflammation focally or diffus			<u> </u>	I
Pneumothorax	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; intervention indicated (e.g., tube placement without sclerosis)	Sclerosis and/or operative intervention indicated; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	red by abnormal presence of air in	the pleural cavity resulting in the o	collapse of the lung.		
Postnasal drip	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characteriz	red by excessive mucous secretion	in the back of the nasal cavity or	throat, causing sore throat and/or	coughing.	1
Productive cough		Moderate sputum production; limiting instrumental ADL	Persistent or copious production of sputum; limiting self care ADL	-	-
	red by expectorated secretions upo		Covere diannes et diannes et	Life threatening requireten.	Dooth
Pulmonary edema	Radiologic findings only; minimal dyspnea on exertion	Moderate dyspnea on exertion; medical intervention indicated; limiting instrumental ADL	Severe dyspnea or dyspnea at rest; oxygen indicated; limiting self care ADL	Life-threatening respiratory compromise; urgent intervention or intubation with ventilatory support indicated	Death
	red by accumulation of fluid in the I				I
Pulmonary fibrosis	Mild hypoxemia; radiologic pulmonary fibrosis <25% of lung volume	Moderate hypoxemia; evidence of pulmonary hypertension; radiographic pulmonary fibrosis 25 - 50%	Severe hypoxemia; evidence of right-sided heart failure; radiographic pulmonary fibrosis >50 - 75%	Life-threatening consequences (e.g., hemodynamic/pulmonary complications); intubation with ventilatory support indicated; radiographic pulmonary fibrosis >75% with severe honeycombing	Death
Definition: A disorder characteriz	red by the replacement of the lung	tissue by connective tissue, leadir	ng to progressive dyspnea, respira	tory failure or right heart failure.	
Pulmonary fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical management indicated; limiting instrumental ADL	Limiting self care ADL; endoscopic stenting or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death

	Respi	ratory, thoracic and med	iastinal disorders		
			Grade	1	1
Adverse Event	1	2	3	4	5
Definition: A disorder characteriz	red by an abnormal communication	between the lung and another or	gan or anatomic site.	1	
Pulmonary hypertension	Minimal dyspnea; findings on physical exam or other evaluation	Moderate dyspnea, cough; requiring evaluation by cardiac catheterization and medical intervention	Severe symptoms, associated with hypoxemia, right heart failure; oxygen indicated	Life-threatening airway consequences; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characteriz	ed by an increase in pressure with	in the pulmonary circulation due to	o lung or heart disorder.		
Respiratory failure	-	-	-	Life-threatening consequences; urgent intervention, intubation, or ventilatory support indicated	Death
Definition: A disorder characteriz with an increase in arterial levels	red by impaired gas exchange by t s of carbon dioxide.	he respiratory system resulting in	hypoxemia and a decrease in oxy	genation of the tissues that may be	e associate
Retinoic acid syndrome	Fluid retention; <3 kg of weight gain; intervention with fluid restriction and/or diuretics indicated	Moderate signs or symptoms; steroids indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; ventilatory support indicated	Death
Definition: A disorder characteriz	zed by weight gain, dyspnea, pleur	al and pericardial effusions, leukoo	cytosis and/or renal failure original	lly described in patients treated wit	h all-trans
Sinus disorder	Asymptomatic mucosal crusting; blood-tinged secretions	Symptomatic stenosis or edema/narrowing interfering with airflow; limiting instrumental ADL	Stenosis with significant nasal obstruction; limiting self care ADL	Necrosis of soft tissue or bone; urgent operative intervention indicated	Death
Definition: A disorder characteriz	red by involvement of the paranasa	al sinuses.	•		
Sleep apnea	Snoring and nocturnal sleep arousal without apneic periods	Moderate apnea and oxygen desaturation; excessive daytime sleepiness; medical evaluation indicated; limiting instrumental ADL	Oxygen desaturation; associated with hypertension; medical intervention indicated; limiting self care ADL	Cardiovascular or neuropsychiatric symptoms; urgent operative intervention indicated	Death
Definition: A disorder characteriz	ed by cessation of breathing for sh	nort periods during sleep.			
Sneezing	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characteriz	ed by the involuntary expulsion of	air from the nose.	'	'	
Sore throat	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL; limiting ability to swallow	-	-
Definition: A disorder characteriz	red by of marked discomfort in the	throat	'	•	•
Stridor	-	-	Respiratory distress limiting self care ADL; medical intervention indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characteriz	red by a high pitched breathing sou	und due to laryngeal or upper airw	ay obstruction.		
Tracheal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention indicated (e.g., thoracoplasty, chronic open drainage or multiple thoracotomies)	Death
Definition: A disorder characteriz	ed by an abnormal communication	between the trachea and another	r organ or anatomic site.		
Tracheal mucositis	Endoscopic findings only; minimal hemoptysis, pain, or respiratory symptoms	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe pain; hemorrhage or respiratory symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
	ted by an inflammation involving th			Ī	I_
Tracheal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Stridor or respiratory distress limiting self care ADL; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
	red by a narrowing of the trachea.	1	1	•	•

	Respi	ratory, thoracic and med	iastinal disorders					
	Grade							
Adverse Event	1	2	3	4	5			
Voice alteration	Mild or intermittent change from normal voice	Moderate or persistent change from normal voice; still understandable	Severe voice changes including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; may require assistive technology	-	-			
Definition: A disorder characteriz	ed by a change in the sound and/o	or speed of the voice.						
Wheezing	Detectable airway noise with minimal symptoms	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe respiratory symptoms limiting self care ADL; oxygen therapy or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteriz	ed by a high-pitched, whistling sou	ind during breathing. It results from	n the narrowing or obstruction of t	he respiratory airways.				
Respiratory, thoracic and mediastinal disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death			

Skin and subcutaneous tissue disorders Grade							
Adverse Event	1	2	3	4	5		
Alopecia	Hair loss of <50% of normal for	Hair loss of >=50% normal for	-	-	-		
	that individual that is not	that individual that is readily					
	obvious from a distance but only	apparent to others; a wig or hair					
	on close inspection; a different	piece is necessary if the patient					
	hair style may be required to	desires to completely					
	cover the hair loss but it does	camouflage the hair loss;					
	not require a wig or hair piece to	associated with psychosocial					
	camouflage	impact					
Definition: A disorder characteriz	zed by a decrease in density of hair	· · compared to normal for a given i	ndividual at a given age and body	location.	•		
Body odor	Mild odor; physician intervention	Pronounced odor; psychosocial	-	_	l -		
,	not indicated; self care	impact; patient seeks medical					
	· ·	intervention					
Definition: A disorder characteris	1	I	I on the hady	I	I		
	zed by an abnormal body smell res			I	I		
Bullous dermatitis	Asymptomatic; blisters covering	Blisters covering 10 - 30% BSA;	Blisters covering >30% BSA;	Blisters covering >30% BSA;	Death		
	<10% BSA	painful blisters; limiting	limiting self care ADL	associated with fluid or			
		instrumental ADL		electrolyte abnormalities; ICU			
				care or burn unit indicated			
Definition: A disorder characteriz	zed by inflammation of the skin cha	racterized by the presence of bulls	ae which are filled with fluid.				
Dry skin	Covering <10% BSA and no	Covering 10 - 30% BSA and	Covering >30% BSA and	-	-		
,		associated with erythema or	associated with pruritus; limiting				
	acconated oryanomia or pramac	pruritus; limiting instrumental	self care ADL				
		ADL	Sell care ADE				
D C ''' A P	1	l	I		l		
Definition: A disorder characteriz	zed by flaky and dull skin; the pores			<u> </u>	1		
Erythema multiforme	Target lesions covering <10%	Target lesions covering 10 -	Target lesions covering >30%	Target lesions covering >30%	Death		
	BSA and not associated with	30% BSA and associated with	BSA and associated with oral or	BSA; associated with fluid or			
	skin tenderness	skin tenderness	genital erosions	electrolyte abnormalities; ICU			
				care or burn unit indicated			
Definition: A disorder characteriz	zed by target lesions (a pink-red rin	g around a pale center).					
Erythroderma		Erythema covering >90% BSA	Erythema covering >90% BSA	Erythema covering >90% BSA	Death		
		without associated symptoms;	with associated symptoms (e.g.,	with associated fluid or	D Guii.		
		limiting instrumental ADL	pruritus or tenderness); limiting	electrolyte abnormalities; ICU			
		initially institutional ABE	self care ADL	care or burn unit indicated			
			'	'	l		
Definition: A disorder characteriz	zed by generalized inflammatory er			f the body surface area.			
Fat atrophy	Covering <10% BSA and	Covering 10 - 30% BSA and	Covering >30% BSA;	-	-		
	asymptomatic	associated with erythema or	associated with erythema or				
		tenderness; limiting instrumental	tenderness; limiting self-care				
					1		
		ADL	ADL	•			
Definition: A disorder characteriz	zed by shrinking of adipose tissue.	ADL	ADL	<u> </u>			
	1	ADL In women, increase in length,	ADL -	-	T-		
Definition: A disorder characteriz Hirsutism	zed by shrinking of adipose tissue. In women, increase in length,	In women, increase in length,	ADL	-	-		
	zed by shrinking of adipose tissue.	In women, increase in length, thickness or density of hair in a	ADL	-	-		
	ln women, increase in length, thickness or density of hair in a male distribution that the patient	In women, increase in length, thickness or density of hair in a male distribution that requires	-	-	-		
	ln women, increase in length, thickness or density of hair in a male distribution that the patient is able to camouflage by	In women, increase in length, thickness or density of hair in a male distribution that requires daily shaving or consistent	-	-	-		
	ln women, increase in length, thickness or density of hair in a male distribution that the patient is able to camouflage by periodic shaving, bleaching, or	In women, increase in length, thickness or density of hair in a male distribution that requires daily shaving or consistent destructive means of hair	-	-	-		
	ln women, increase in length, thickness or density of hair in a male distribution that the patient is able to camouflage by	In women, increase in length, thickness or density of hair in a male distribution that requires daily shaving or consistent destructive means of hair removal to camouflage;	- -	-	-		
	ln women, increase in length, thickness or density of hair in a male distribution that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair	In women, increase in length, thickness or density of hair in a male distribution that requires daily shaving or consistent destructive means of hair removal to camouflage; associated with psychosocial	-	-	-		
Hirsutism	ln women, increase in length, thickness or density of hair in a male distribution that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair	In women, increase in length, thickness or density of hair in a male distribution that requires daily shaving or consistent destructive means of hair removal to camouflage; associated with psychosocial impact	-	-	-		
-lirsutism Definition: A disorder characteriz	ln women, increase in length, thickness or density of hair in a male distribution that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair	In women, increase in length, thickness or density of hair in a male distribution that requires daily shaving or consistent destructive means of hair removal to camouflage; associated with psychosocial impact	-	e a secondary male characteristic	- c and und		
Hirsutism Definition: A disorder characteriz androgen control (beard, mousta	In women, increase in length, thickness or density of hair in a male distribution that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair	In women, increase in length, thickness or density of hair in a male distribution that requires daily shaving or consistent destructive means of hair removal to camouflage; associated with psychosocial impact growth in women in anatomic site	s where growth is considered to b	e a secondary male characteristic	- c and und		
Hirsutism Definition: A disorder characteriz androgen control (beard, mousta	In women, increase in length, thickness or density of hair in a male distribution that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair	In women, increase in length, thickness or density of hair in a male distribution that requires daily shaving or consistent destructive means of hair removal to camouflage; associated with psychosocial impact growth in women in anatomic site	s where growth is considered to b	e a secondary male characteristic	- and und		
Hirsutism Definition: A disorder characteriz androgen control (beard, mousta	In women, increase in length, thickness or density of hair in a male distribution that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair	In women, increase in length, thickness or density of hair in a male distribution that requires daily shaving or consistent destructive means of hair removal to camouflage; associated with psychosocial impact growth in women in anatomic site	s where growth is considered to b	e a secondary male characteristic	- and und		
Hirsutism	In women, increase in length, thickness or density of hair in a male distribution that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair	In women, increase in length, thickness or density of hair in a male distribution that requires daily shaving or consistent destructive means of hair removal to camouflage; associated with psychosocial impact growth in women in anatomic site	s where growth is considered to b	e a secondary male characteristic	- c and und		
Hirsutism Definition: A disorder characteriz androgen control (beard, mousta	In women, increase in length, thickness or density of hair in a male distribution that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair Led by the presence of excess hair ache, chest, abdomen) Limited to one site (palms, soles, or axillae); self care	In women, increase in length, thickness or density of hair in a male distribution that requires daily shaving or consistent destructive means of hair removal to camouflage; associated with psychosocial impact growth in women in anatomic site Involving >1 site; patient seeks medical intervention; associated	s where growth is considered to b Generalized involving sites other than palms, soles, or	e a secondary male characteristic	- and und		

Skin and subcutaneous tissue disorders Grade							
Advance Event	4	2	Grade 3	4	5		
Adverse Event Hypertrichosis	Increase in length, thickness or density of hair that the patient is either able to camouflage by periodic shaving or removal of hairs or is not concerned enough about the overgrowth to use any form of hair removal	Increase in length, thickness or density of hair at least on the usual exposed areas of the body [face (not limited to beard/moustache area) plus/minus arms] that requires frequent shaving or use of	-	-	-		
Definition: A disorder characteri.	zed by hair density or length beyon	destructive means of hair removal to camouflage; associated with psychosocial impact d the accepted limits of normal in	a particular body region, for a part	icular age or race.			
Hypohidrosis	-	Symptomatic; limiting instrumental ADL	Increase in body temperature; limiting self care ADL	Heat stroke	Death		
Definition: A disorder characteri.	zed by reduced sweating.	Т	1	Т	1		
Lipohypertrophy	Asymptomatic and covering <10% BSA	Covering 10 - 30% BSA and associated tenderness; limiting instrumental ADL	Covering >30% BSA and associated tenderness and narcotics or NSAIDs indicated; lipohypertrophy; limiting self care ADL	-	-		
Definition: A disorder characteri.	zed by hypertrophy of the subcutan	eous adipose tissue at the site of	multiple subcutaneous injections of	of insulin.			
Nail discoloration	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-		
Definition: A disorder characterize	zed by a change in the color of the	nail plate.	T	Γ	ı		
Nail Ioss	Asymptomatic separation of the nail bed from the nail plate or nail loss	Symptomatic separation of the nail bed from the nail plate or nail loss; limiting instrumental ADL	-	-	-		
Definition: A disorder characteri:	zed by loss of all or a portion of the	nail.	_	T			
Nail ridging	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-		
Definition: A disorder characteri:	zed by vertical or horizontal ridges	on the nails.		•			
Pain of skin	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-		
Definition: A disorder characterize	zed by marked discomfort sensation				T		
Palmar-plantar erythrodysesthesia syndrome	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain zed by redness, marked discomfort	Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL	Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self care ADL		-		
	1			eet.			
Periorbital edema	Soft or non-pitting	Indurated or pitting edema; topical intervention indicated	Edema associated with visual disturbance; increased intraocular pressure, glaucoma or retinal hemorrhage; optic neuritis; diuretics indicated; operative intervention indicated		-		
Definition: A disorder characteri:	zed by swelling due to an excessive	e accumulation of fluid around the	orbits of the face.	I	1		
Photosensitivity	Painless erythema and erythema covering <10% BSA	Tender erythema covering 10 - 30% BSA	Erythema covering >30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (e.g., narcotics or NSAIDs)	Life-threatening consequences; urgent intervention indicated	Death		

Skin and subcutaneous tissue disorders								
Grade								
Adverse Event	1	2	3	4	5			
Pruritus	Mild or localized; topical intervention indicated	Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Intense or widespread; constant; limiting self care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated	-	-			
Definition: A disorder character	ized by an intense itching sensation		ı	I	'			
Purpura	Combined area of lesions covering <10% BSA	Combined area of lesions covering 10 - 30% BSA; bleeding with trauma	Combined area of lesions covering >30% BSA; spontaneous bleeding	- Dider lesions are usually a darker	- purple color			
and eventually become a brown				,				
Rash acneiform	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; lifethreatening consequences	Death			
Definition: A disorder character	ized by an eruption of papules and p	, oustules, typically appearing in fac	e, scalp, upper chest and back.	'	•			
Rash maculo-papular	Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering >30% BSA with or without associated symptoms; limiting self care ADL	-	-			
	ized by the presence of macules (fla upper trunk, spreading centripetally		nown as morbillform rash, it is one	of the most common cutaneous a	dverse			
Scalp pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder character	ized by marked discomfort sensation	n in the skin covering the top and	the back of the head.	ř				
Skin atrophy	Covering <10% BSA; associated with telangiectasias or changes in skin color	Covering 10 - 30% BSA; associated with striae or adnexal structure loss	Covering >30% BSA; associated with ulceration	-	-			
Definition: A disorder character	ized by the degeneration and thinnir	ng of the epidermis and dermis.		T				
Skin hyperpigmentation	Hyperpigmentation covering <10% BSA; no psychosocial impact	Hyperpigmentation covering >10% BSA; associated psychosocial impact	-	-	-			
Definition: A disorder character	ized by darkening of the skin due to	excessive melanin deposition.						
Skin hypopigmentation	Hypopigmentation or depigmentation covering <10% BSA; no psychosocial impact	Hypopigmentation or depigmentation covering >10% BSA; associated psychosocial impact	-	-	-			
Definition: A disorder character	ized by loss of skin pigment.							
Skin induration	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration, unable to slide or pinch skin; limiting joint movement or orifice (e.g., mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death			
Definition: A disorder character	ized by an area of hardness in the s		T	Γ				
Skin ulceration	Combined area of ulcers <1 cm; nonblanchable erythema of intact skin with associated warmth or edema	Combined area of ulcers 1 - 2 cm; partial thickness skin loss involving skin or subcutaneous fat	Combined area of ulcers >2 cm; full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may	Any size ulcer with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures with or	Death			

Skin and subcutaneous tissue disorders							
		Grade					
Adverse Event	1	2	3	4	5		
Stevens-Johnson syndrome	-	-	Skin sloughing covering <10% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment)	Skin sloughing covering 10 - 30% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment)	Death		
Definition: A disorder characterize mucous membranes.	ed by less than 10% total body ski	n area separation of dermis. The	syndrome is thought to be a hyper	rsensitivity complex affecting the s	kin and the		
Telangiectasia	Telangiectasias covering <10% BSA	Telangiectasias covering >10% BSA; associated with psychosocial impact	-	-	-		
Definition: A disorder characterize	ed by local dilatation of small vess	els resulting in red discoloration o	f the skin or mucous membranes.	1			
Toxic epidermal necrolysis	-	-	-	Skin sloughing covering >=30% BSA with associated symptoms (e.g., erythema, purpura, or epidermal detachment)	Death		
Definition: A disorder characterize mucous membranes.	ed by greater than 30% total body	skin area separation of dermis. T	he syndrome is thought to be a hy	persensitivity complex affecting th	e skin and the		
Urticaria	Urticarial lesions covering <10% BSA; topical intervention indicated	Urticarial lesions covering 10 - 30% BSA; oral intervention indicated	Urticarial lesions covering >30% BSA; IV intervention indicated	-	-		
Definition: A disorder characterize	ed by an itchy skin eruption charac	cterized by wheals with pale interio	ors and well-defined red margins.				
Skin and subcutaneous tissue disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death		

Social circumstances							
			Grade				
Adverse Event	1	1 2 3 4 5					
Menopause	Menopause occurring at age 46 - 53 years of age	Menopause occurring at age 40 - 45 years of age	Menopause occurring before age 40 years of age	-	-		
Definition: A disorder characteriz	ed by the permanent cessation of	menses, usually defined by 12 co	nsecutive months of amenorrhea i	n a woman over 45 years of age.			
Social circumstances - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated;	Life-threatening consequences; urgent intervention indicated	Death		
			disabling; limiting self care ADL				

Surgical and medical procedures						
		Grade				
Adverse Event	1	2	3	4	5	
Surgical and medical	Asymptomatic or mild	Moderate; minimal, local or	Severe or medically significant	Life-threatening consequences;	Death	
procedures - Other, specify	symptoms; clinical or diagnostic	noninvasive intervention	but not immediately life-	urgent intervention indicated		
	observations only; intervention	indicated; limiting age-	threatening; hospitalization or			
	not indicated	appropriate instrumental ADL	prolongation of existing			
			hospitalization indicated;			
I			disabling; limiting self care ADL			

Vascular disorders					
			Grade		
Adverse Event	1	2	3	4	5
Capillary leak syndrome	-	Symptomatic; medical intervention indicated	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	ed by leakage of intravascular fluid syndromes, low-flow states, ischer			-	
Flushing	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Symptomatic, associated with hypotension and/or tachycardia; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by episodic reddening of the fa	ce.	1	1	1
Hematoma	Mild symptoms; intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by a localized collection of bloc	od, usually clotted, in an organ, sp	ace, or tissue, due to a break in th	e wall of a blood vessel.	
Hot flashes	Mild symptoms; intervention not indicated	instrumental ADL	Severe symptoms; limiting self care ADL	-	-
	ed by an uncomfortable and temp	orary sensation of intense body wa T	armth, flushing, sometimes accom		1
Hypertension	Prehypertension (systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg)	Stage 1 hypertension (systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg); medical intervention indicated; recurrent or persistent (>=24 hrs); symptomatic increase by >20 mm Hg (diastolic) or to	Stage 2 hypertension (systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated Pediatric: Same as adult	Death
		>140/90 mm Hg if previously WNL; monotherapy indicated Pediatric: recurrent or persistent (>=24 hrs) BP >ULN; monotherapy indicated	Pediatric: Same as adult		
Definition: A disorder characteriz	ed by a pathological increase in bl		,	ľ	1
Hypotension	indicated	Non-urgent medical intervention indicated	hospitalization indicated	Life-threatening and urgent intervention indicated	Death
Definition: A disorder characteriz	ed by a blood pressure that is belo	ow the normal expected for an indi	ividual in a given environment.	1	
Lymph leakage	-	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by the loss of lymph fluid into the	ne surrounding tissue or body cavi	ity.	1	1
Lymphedema	Trace thickening or faint discoloration	Marked discoloration; leathery skin texture; papillary formation; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by excessive fluid collection in	tissues that causes swelling.			
Lymphocele	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	-	-
Definition: A disorder characteriz	ed by a cystic lesion containing ly	nph.	1		
Peripheral ischemia	-	Brief (<24 hrs) episode of ischemia managed non- surgically and without permanent deficit	Recurring or prolonged (>=24 hrs) and/or invasive intervention indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A disorder characteriz	ed by impaired circulation to an ex	tremity.		_	
Phlebitis	-	Present	-	-	-
Definition: A disorder characteriz	ed by inflammation of the wall of a	vein. Present	-	-	-
	। ed by a blood clot and inflammatic	1	e extremities.	1	1

Vascular disorders					
			Grade		
Adverse Event	1	2	3	4	5
Superior vena cava syndrome	Asymptomatic; incidental finding of SVC thrombosis	Symptomatic; medical intervention indicated (e.g., anticoagulation, radiation or chemotherapy)	Severe symptoms; multi- modality intervention indicated (e.g., anticoagulation, chemotherapy, radiation, stenting)	Life-threatening consequences; urgent multi-modality intervention indicated (e.g., lysis, thrombectomy, surgery)	Death
Definition: A disorder characterize cough, orthopnea and headache.	ed by obstruction of the blood flow	in the superior vena cava. Signs	and symptoms include swelling ar	nd cyanosis of the face, neck, and	upper arms,
Thromboembolic event	Venous thrombosis (e.g., superficial thrombosis)	Venous thrombosis (e.g., uncomplicated deep vein thrombosis), medical intervention indicated	Thrombosis (e.g., uncomplicated pulmonary embolism [venous], non-embolic cardiac mural [arterial] thrombus), medical intervention indicated	Life-threatening (e.g., pulmonary embolism, cerebrovascular event, arterial insufficiency); hemodynamic or neurologic instability; urgent intervention indicated	Death
Definition: A disorder characterize	ed by occlusion of a vessel by a th	rombus that has migrated from a	distal site via the blood stream.	.	
Vasculitis	Asymptomatic, intervention not indicated	Moderate symptoms, medical intervention indicated	Severe symptoms, medical intervention indicated (e.g., steroids) Life-threatening; evidence peripheral or visceral ische urgent intervention indicate		Death
Definition: A disorder characterize	ed by inflammation involving the w	rall of a vessel.	•	•	
Visceral arterial ischemia	-	Brief (<24 hrs) episode of ischemia managed medically and without permanent deficit	Prolonged (>=24 hrs) or recurring symptoms and/or invasive intervention indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A disorder characterize	ed by a decrease in blood supply o	due to narrowing or blockage of a	visceral (mesenteric) artery.		
Vascular disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death







NIH Publication No. 09-5410 Revised June 2010 Reprinted June 2010



APPENDIX 2. PEMPHIGUS DISEASE AREA INDEX (PDAI)

Pemphigus Disease Area Index (PDAI)

Skin	Activity		Damage
Anatomical Locatio	Erosion/Blisters or new erythem	а	Post-inflammatory hyperpigmentation or erythema from resolving lesion
	absent 1-3 lesions, up to one >2 cm in any diameter, none > 6 cm 2-3 lesions, at least two > 2 cm diameter, none > 6 cm 3 lesions, none > 6 cm diameter 3 lesions, none > 6 cm diameter 3 lesions, and/or at least one >6 cm 3 lesions, and/or at least one lesion >16 cm diameter or entire area	Number lesions if ≤ 3	0 absent 1 present
Ears			
Nose			
Rest of the face			
Neck			
Chest			
Abdomen			
Back, buttocks			
Arms			12
Hands			4
Legs			
Feet			
Genitals			
Total skin	/120		/12
Scalp	,		
Scalp	Erosion/Blisters or new erythema		Post-inflammatory hyperpigmentation or erythema from resolving lesion 0 absent
	0 absent 1 in one quadrant 2 two quadrants 3 three quadrants 4 affects whole skull 10 at least one lesion > 6 cm		1 present
Total Scalp (0-10)	/10		/1
Mucous mer	nbrane		915
Anatomical Location	Erosion/Blisters		
	0 absent 1 1 lesion 2 2-3 lesions 5 >3 lesions or 2 lesions >2 cm 10 entire area	Number lesions if ≤ 3	
Eyes			
Nose			
Buccal mucosa			
Hard palate			
Soft palate			
Upper gingiva			
Lower gingiva			
Tongue			
Floor of mouth			
Labial bucosa			
Posterior pharynx			
Anogenital			
Total Mucosa	/120		

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APPENDIX 3. AUTOIMMUNE BULLOUS DISEASE QUALITY OF LIFE (ABQOL) QUESTIONNAIRE

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ABQOL Questionnaire

Name:	Date:
DOB: Sex: M/F	Contact Number:
Pemphigus Subtype: Pemphigus Vulgaris	 Epidermolysis Bullosa Aquisita
□ Bullous Pemphigoid	□ Linear IgA Bullous Dermatoses
□ Pemphigus Follaceus	□ Mucous Membrane Pemphigoid
□ Other	·
The following questions ask about the ways in quality of life.	which <i>blistering disease treatments</i> affect your
Please choose an option from the right hand co felt within the last week.	olumn which most closely correlates to how you
Please time your survey in minutes and se	conds – start time AM/PM
 In regards to your blistering disease, does your skin burn, sting or hurt in 	All the time Sometimes
any way?	Occasionally Not at all
2. In regards to your blistering disease,	All the time
does your skin itch?	SometimesOccasionally
	Not at all
Have you had to change your clothing because of your blictoring	I have to be very careful with how tight my elething is and what materials they
clothing because of your blistering disease?	my clothing is and what materials they are made of – I have had to change what I wear all the time
	I have had to change most of the things I wear
	I have had to change some of the things I wear
	I have never had to change what I wear
4. Do you notice your skin heals slowly?	I notice this all the time I notice this sometimes
	I notice this occasionally
Do you have difficulty bathing or	
showering because of your blistering	o Sometimes
disease?	Occasionally Not at all

In regards to your blistering disease, does your mouth have erosions which are painful?	All the timeSometimesOccasionallyNot at all
7. In regards to your blistering disease, do your gums bleed easily?	 All the time Sometimes Occasionally Not at all
Does your blistering disease results in you having to avoid food or drinks that you enjoy?	I can no longer eat any of the foods I used to enjoy I can eat some of the foods I enjoy I can eat most of the foods I enjoy I can eat anything I like
9. As a result of your blistering disease, are you embarrassed about your appearance?	 All the time Sometimes Occasionally Not at all
10. Do you feel depressed or angry because of your blistering disease?	 All the time Sometimes Occasionally Not at all
11. Do you feel anxious or cannot relax as a result of your blistering disease?	 All the time Sometimes Occasionally Not at all
12. Do you worry that friends and family find your blistering skin condition tiresome?	 All the time Sometimes Occasionally Not at all
13. Is your blistering disease causing sexual difficulties?	 All the time Sometimes Occasionally Not at all
14. Does your blistering disease affect relationships with friends or loved ones?	 I have had to end a relationship because of my disease OR I cannot have a relationship because of my disease Relationships are very difficult Relationships are a little difficult This has not affected my relationships

15. Does your blistering disease affect your social life?	 I cannot go out to socialize any more I can only go to some social events I can go to most social events My social life is not affected
16. Does your blistering disease affect your work or study?	 Yes, I can no longer work or study Yes, I find it difficult to work or study Yes, it is a little harder than before to work or study No, I am not affected OR not applicable (N/A)
17. Do employers discriminate against you because of your blistering disease?	 I cannot find a job due to my blistering disease I have had to change jobs due to my blistering disease I still have my job but it is more difficult than before My employers are completely understanding OR not applicable (N/A)

Please indicate the time taken to finish the survery: minutes seconds

Thank you for taking the time to complete this questionnaire

APPENDIX 4. SKINDEX-29

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DERMATOLOGY SURVEY

This survey concerns the skin condition which has bothered you the most during the past four weeks.

These questions concern your feelings over the past 4 weeks about **the skin condition that has bothered you the most**. Check the answer that comes closest to the way you have been feeling.

HOW OFTEN DURING THE PAST FOUR WEEKS DO THESE STATEMENTS DESCRIBE YOU?	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE TIME
1. My skin hurts	1	\square_2	Пз	□4	□5
2. My skin condition affects how well I sleep	\square_1	\square_2	\square_3	\square_4	\square_5
3. I worry that my skin condition may be serious	\square_1	\square_2	\square_3	\square_4	□5
4. My skin condition makes it hard to work or do hobbies	□₁	\square_2	\square_3	\square_4	\square_5
5. My skin condition affects my social life	\square_1	\square_2	\square_3	\square_4	□5
6. My skin condition makes me feel depressed	\square_1	\square_2	\square_3	\square_4	□5
7. My skin condition burns or stings	\square_1	\square_2	\square_3	\square_4	□5
8. I tend to stay at home because of my skin condition	\square_1	\square_2	\square_3	\square_4	\square_5
9. I worry about getting scars from my skin condition	\square_1	\square_2	Пз	\square_4	\square_5
10. My skin itches	\square_1	\square_2	Пз	\square_4	\square_5
11. My skin condition affects how close I can be with those I love .	\square_1	\square_2	Пз	\square_4	\square_5
12. I am ashamed of my skin condition	\square_1	\square_2	\square_3	\square_4	\square_5
13. I worry that my skin condition may get worse	\square_1	\square_2	Пз	\square_4	\square_5
14. I tend to do things by myself because of my skin condition .	\square_1	\square_2	Пз	\square_4	\square_5
15. I am angry about my skin condition	\square_1	\square_2	Пз	\square_4	\square_5
16. Water bothers my skin condition (bathing, washing hands) .	\square_1	\square_2	Пз	\square_4	\square_5
17. My skin condition makes showing affection difficult	\square_1	\square_2	Пз	\square_4	\square_5
18. I worry about side-effects from skin medications / treatments .	\square_1	\square_2	Пз	\square_4	\square_5
19. My skin is irritated	□1	\square_2	Пз	\square_4	\square_5
20. My skin condition affects my interactions with others	□1	\square_2	\square_3	\square_4	□5

Please turn to next page

These questions concern your feelings over the past 4 week about **the skin condition that has bothered you the most**. Check the answer that comes closest to the way you have been feeling.

HOW OFTEN DURING THE PAST 4 WEEK DO THESE STATEMENTS DESCRIBE YOU?		RARELY	SOMETIMES	OFTEN	ALL THE TIME
21. I am embarrassed by my skin condition	□ 1	\square_2	Пз	□4	□5
22. My skin condition is a problem for the people I love	□₁	\square_2	\square_3	\square_4	\square_5
23. I am frustrated by my skin condition	□₁	\square_2	\square_3	\square_4	\square_5
24. My skin is sensitive	□₁	\square_2	\square_3	\square_4	\square_5
25. My skin condition affects my desire to be with people	□₁	\square_2	\square_3	\square_4	\square_5
26. I am humiliated by my skin condition	□1	\square_2	\square_3	\square_4	\square_5
27. My skin condition bleeds	□₁	\square_2	\square_3	\square_4	\square_5
28. I am annoyed by my skin condition	□₁	\square_2	\square_3	\square_4	\square_5
29. My skin condition interferes with my sex life	□₁	\square_2	\square_3	\square_4	\square_5
30. My skin condition makes me tired	□₁	\square_2	\square_3	\square_4	\square_5

PROTOCOL AMENDMENT **SUMMARY OF CHANGES**

Protocol Title: Phase 1b/2 Multicenter, Open-Label, Safety, and Dose-Finding Study

of SYNT001 in Subjects with Pemphigus (Vulgaris or Foliaceus)

Protocol Number: SYNT001-103

Study Drug: SYNT001

Syntimmune, Inc. **Sponsor:**

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Original Protocol 18 January 2017 1.0 21 March 2017 12 April 2017 2.0 10 October 2017 3.0 08 June 2018 4.0

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BACKGROUND

Protocol amendment Version 4.0 of the SYNT001-103 protocol was issued on 07 June 2018.

Since the design of the original protocol, the Sponsor has completed longer SYNT001 nonclinical toxicology studies (14-weeks vs 5-weeks). Additionally, the Sponsor has gained experience with conducting the trial and has learned about logistical issues affecting the successful execution of the protocol to obtain preliminary safety and effectiveness data.

For a number of reasons, including inclusion and exclusion criteria, prohibited and permitted medications, and logistical burden of study conduct (eg, number and complexity of study visits), enrollment into study SYNT001-103 has been far slower than anticipated. Further, as currently designed, the study will provide only limited information on dose selection to support further clinical development (eg, duration of dosing and potential role of a loading dose approach cannot be assessed). Preliminary safety results support good safety and tolerability of SYNT001 at 10 mg/kg for 5 weekly doses. Regarding efficacy, data thus far support proof-of-concept for SYNT001 in pemphigus; however, it appears that longer dosing will be needed to maintain response and higher doses may lead to a higher response rate and robustness of response.

Syntimmune therefore is amending the SYNT001-103 protocol to address the above issues. The Study Assessments have been extensively modified to decrease the complexity of the study and make the execution of the study more acceptable to potential subjects and more feasible for study sites; changes include the removal of 7 study visits and organization of study visits into major and minor visits with more consistent assessments. It is anticipated that these changes should facilitate study enrollment, especially when combined with additional adjustments to the inclusion and exclusion criteria and prohibited medications, including removal of the upper limit on body mass index (previously was 39.9 kg/m²) and allowance for steroid tapering prior to screening. To better inform dose selection and pivotal trial design, dosing in Cohort 3 has been extended from 5 weekly doses to 14, and an optional Cohort 4 has been added to allow exploration of an alternate dose level (maximum of 45 mg/kg) and dosing duration (up to 14 weekly doses) to be determined following data review by the Dose Escalation Committee (DEC). This option could include a loading dose followed by lower weekly doses. To gain more information on dose selection, endpoints regarding extent of lowering of total IgG levels and change in the Pemphigus Disease Area Index (PDAI) total activity score from baseline have been added as a primary objective in addition to safety.

Administrative changes in the amendment include changes in the medical monitor and Sponsor contact information. General grammatical, typographical, and formatting updates have been made throughout the document to provide consistency and clarity, reduce redundancy, and improve readability.

SUMMARY OF CHANGES

With this update, the following changes since Version 3.0 have been made:

 Table 1.
 Summary of Changes: Protocol Version 4.0

Section	Description of Change
Number and Title	
Cover Page	Protocol Title
	• Revised to indicate updated Phase 1b/2 status and dose finding intent to commence under Cohorts 2, 3, and optional Cohort 4.
	• Removed tolerability as a quantifiable measurement as the focus of the trial will be safety.
	 Medical term for primary indication revised from chronic pemphigus to pemphigus to more closely reflect eligibility criteria and terminology commonly used by treating physicians.
	Other
	The Medical Monitor's title and Syntimmune Inc. address have been updated for accuracy.
Section 1, Protocol Synopsis	The protocol synopsis has been modified to more closely align with industry standards and the National Institute of Health (NIH)/Food and Drug Administration (FDA) protocol template. Below is a summary of changes; refer to the changes described for the individual protocol sections for more detail:
	Added the sponsor, Syntimmune Inc.
	 Indicated the company's intentions to open study sites outside the United States of America to support subject enrollment.
	 The study rationale is now an overview of protocol Section 2, Background and Rationale.
	 Study objectives have been grouped with study endpoints; study objectives now only appear once in the protocol synopsis.
	 The study design not only describes changes to cohorts but now includes the role of the Dose Escalation Committee (DEC) and stopping and dose escalation rules.
	• Study methodology has been separated from study design and is now in a stand-alone section.
	• The inclusion and exclusion criteria have been modified as described in Section 6 Study Population.
	 Additional detail has been added to Duration of subject participation and Study drug, dosage, and administration.
	 Prohibited Concomitant treatments has now been changed to Permitted and Prohibited Concomitant Treatments.

	• The following sections have been removed from the synopsis, but content remains in the protocol text to reduce redundancy:
	 Safety assessments
	o Pharmacokinetics
	o Pharmacodynamics/Activity
	o Immunogenicity
	 Skin biopsy
	o Photography
	• In the statistical consideration section, the intent to treat (ITT) study population has been changed to Safety population. Analyses have been updated to reflect additional detail included in the study endpoints.
	 Subheadings have been added to clearly delineated content.
Study Diagram	Study Diagram has been added changing the dose, number of doses and timing of DEC reviews for Cohorts 2 and 3 and adding optional Cohort 4 to reflect changes to study design.
	• Cohort 1 number of subjects has been modified from 8 to up to 8.
	• Cohort 2 dose has been modified to ≤30 mg/kg and the number of subjects reduced from 8 to 4.
	• Cohort 3 has been added with ≤ 30 mg/kg and number of doses extended to 14 in 4 subjects.
	• The optional cohort has shifted from Cohort 3 to 4 with a maximum dose of 45 mg/kg and maximum number of doses out to 14.
	• Timing of DEC data reviews for Cohorts 2 and 3 is after 50% of subjects reach Day 42.
	• The DEC may now lower the dose within a cohort and add up to 4 additional patients to Cohorts 2, 3, and optional Cohort 4.
Schedule of	Table 3 (Cohort 2)
Events	• Efforts were made to simplify the study of events to reduce subject and site burden and increase flexibility with visit scheduling, as described below:
	 A total of 7 visits have been removed (Days 1, 2, 5, 12, 19, 29, and 20).
	 Day 33 has been changed to Day 35 to shift to a weekly visit schedule out to 1 month after the final dose.
	 Visit windows have been increased as outlined below:
	■ Weekly visits: ± 1 day
	■ Every other week visit: ± 3 days
	■ Monthly visits: ± 5 days
	• Specific changes to the Schedule of Events as compared to Cohort 1 (Table 2) are described below. Many of the changes support

categorization of Treatment and Follow-up visits into major and minor visits. All minor visits have the same schedule of testing. Tests conducted at major visits are now more consistent.

- Pemphigus Disease Area Index (PDAI), physical examination, and anti-desmoglein (1 and 3) antibody titers are being done at every visit.
- Tetanus and Varicella Zoster testing will now be done at set timepoints (Baseline, Day 56, and Day 112).
- Pharmacokinetic (PK) sampling will only be done at Baseline and the day of the final SYNT001 final dose.
- o Immunogenicity is no longer done at Day 84.
- Testing of biomarkers has been reduced [complement component 3 (C3), anti-epithelial cell antibody (AECA), RNAseq, urine immunoglobulin G (IgG), and immunophenotyping]. These biomarkers are now only done at Baseline, Day 35, and Day 56.
- o Photography is no longer done at Day 14 and Day 84.
- o Added Health-related Quality of Life (HR-QoL) questionnaires to Baseline, Day 35, Day 56, and Day 112.

Table 4 (Cohort 3)

- Assessments done at Screening, Baseline and Follow-up visits align with Cohort 2 (Table 3).
- Treatment will extend from 5 to 14 doses and subjects will receive weekly IV infusions during this time.
 - Assessments at the mid-point of dosing and the final dose (major visits) align with Cohort 2 (Table 3).
 - Assessments at all other treatment visits (minor visits) also align with Cohort 2 (Table 3).

Table of Contents

The overall structure of the document has been modified slightly to improve readability and usability:

- Study Objectives and Endpoints have been logically grouped together under Section 3.0.
- Study Drug section has been moved up in the protocol due to its importance and now falls directly after Study Objectives and Endpoints. The content has not fundamentally changed but has been organized into recognizable sections for easy reference.
- The order of Study Procedures in Section 7 now more closely reflects the Schedule of Events.
- A section has been added for HR-QoL questonnaires to mirror the updated Schedule of Events.
- Study Assessments section now details Cohort 2 Schedule of Events and the extended dosing out to 14 doses for Cohort 3.

	Section 9 title has been changed from Removing Subjects from Study to Study Rules. Lost to Follow-up was added as a sub-section.
	• The Safety section has been reorganized for improved readability and now includes the Procedures in Case of Emergency that was previously at the start of the document.
	• Vaccinations, Management of Allergic or Infusion Reactions, and Potential Immune Effects are grouped under Warnings and Precautions (Section 10.3).
	• Overdose has been added to Other Safety Considerations (Section 10.5).
	• Multiple sections were collapsed into 1 comprehensive section titled Study Management (Section 12).
	Tables have been added to reflect the new study design and assessments by cohort.
	• Appendices have been added for the new HR-QoL questionnaires, the Autoimmune Bullous Disease Quality of Life (ABQoL) and Skindex-29.
	Figure 1 was added to illustrate the study design.
List of Abbreviations	The table was updated to include all abbreviations throughout the synopsis and protocol text. Each abbreviation was defined the first time used in both the synopsis and protocol text.
Section 2,	Background and Rationale
Background and Rationale	• Text has been added to describe SYNT001's predicted mechanism of action.
	Additional indications identified as IgG-mediated autoimmune disorders have been added.
	Study Rationale
	The study rationale has been updated to include dose activity criteria and remove tolerability criteria.
	Selection of Doses in this Study
	Non-human primate (NHP) data is now described before the healthy volunteer study (Phase 1a) to follow the chronology of when the studies completed. Information about the completed 14-week toxicology study has been added.
Section 3, Study	Study objectives and endpoints have not fundamentally changed but
Objectives and	have been rewritten to more closely align with industry standards.
Endpoints	An objective and endpoint have been added for dose selection to define pritorio to select a dose for future eliminal testing.
	 criteria to select a dose for future clinical testing. Edits have been made to ensure each objective has a corresponding
	endpoint and vice versa.

	A 11 / 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
	• An objective and endpoint have been added for the HR-QoL questionnaires; the HR-QoL will be used to better understand the
	subject experience when being dosed with SYNT001.
Section 4, Study	Description of SYNT001
Drug	 Windows for the SYNT001 infusion duration (±15 minutes) have been
Drug	added to account for procedural and patient differences.
	Dose Requirements
	It has been clarified that subject doses will be limited to 5000 mg. A
	subject with a body weight that extrapolates to a dose > 5000 mg, will
	only receive 5000 mg.
Section 5, Study	The study design has been updated to reflect changes in dose, number of
Design	doses and timing of DEC reviews for Cohorts 2 and 3 and adding optional
8	Cohort 4.
	• Cohort 1 number of subjects modified from 8 to up to 8.
	• Cohort 2 dose modified to < 30 mg/kg and reduced the number of
	subjects from 8 to 4.
	• Cohort 3 has been added with ≤ 30 mg/kg and number of doses to 14 in
	4 subjects.
	• The optional cohort has shifted from Cohort 3 to 4 with a maximum
	dose of 45 mg/kg and maximum doses out to 14.
	• Timing of DEC Data Reviews for Cohorts 2 and 3 is after 50% of
	subjects reach Day 42.
	• The DEC may now lower the dose within a cohort and add up to 4
	additional patients in to Cohorts 2, 3, and optional Cohort 4.
	Study Rules were not included, as done in the corresponding synopsis
	section; instead Section 9 (Study Rules) is referenced.
Section 6, Study	Target Population
Population	Based on the new study design, the total number of subjects has been
	updated to 20 with a possible additional 12 subjects pending DEC
	evaluation.
	o Enrollment into Cohort 2 onwards revised from 8 to 4 subjects
	with an additional optional 4 subjects per cohort pending DEC
	evaluation.
	Inclusion Criteria
	• #4b. Expanded list of concomitant immunosuppressants to include
	methotrexate, dapsone, cyclosporine, tacrolimus, sirolimus,
	cyclophosphamide. Parameter of stable dose raised from <10% to
	<25% change in dose and window narrowed from 6 weeks to 4 weeks
	prior to screening.
	• #4c. Change in dose of concomitant corticosteroids considered
	acceptable during the 2 weeks prior to screening changed from a 10%
	change in dose to an increase in dose by 50%.

- #4d. Expanded list of allowable topical therapies for pemphigus lesions to include low-strength hydrocortisone (≤ 1%), tacrolimus, sirolimus, pimecrolimus, and dexamethasone elixir solution.
- #4e. If not on regular corticosteroids, no pulse corticosteroids are allowed in the 2 weeks prior to screening.
- #5. Eliminated upper body mass index (BMI) limit of 39.9 kg/m².
- #10. Added a PDAI total severity score of >4 at screening.

Exclusion Criteria

- #6. Reduced intravenous immunoglobulin (IVIG) treatment window prior to screening from 60 days to 30 days.
- #9. Reduced plasmapheresis or immunoadsorption treatment window prior to screening from 60 to 30 days.
- #11. Clarified that systemic or topical immunosuppressive drugs are excluded unless specified in the inclusion criteria.

Section 7, Study Procedures

- Pulse oximetry has been included under vital sign measurements.
- Table 6 with timing windows for PK/pharmacodynamic (PD) Sampling, electrocardiogram (ECG), and Vital Sign Measure has been moved to the Study Procedures Section.
 - The timing windows for Cohorts 2, 3, and optional Cohort 4 were added.
 - Windows were separated from the pharmacokinetic sampling windows.
- RR Interval as a required part of the ECG assessments has been added back into the protocol.
- Blood volumes for clinical laboratory measurements have been recalculated to align with changes to the Schedule of Events.
- Serum tetanus antibody and varicella-zoster virus antibody testing has been simplified and will be done at set timepoints.
- For Cohorts 2, 3, and optional Cohort 4, PK parameters studied will be maximum plasma concentration determined directly from the concentration-time profile (C_{max}) and observed time to reach peak plasma concentration (T_{max}).
- Pharmacodynamic Assessment (Table 8) has been updated to include timing of testing for Cohorts 2 and 3.
- Clarified that immunogenicity testing will also include determination of anti-drug antibody (ADA) titer.
- Section for HR-QoL questionnaires has been added to mirror the updated Schedule of Events.
- Optional skin biopsies will not be collected after Cohort 1.

Prior and Concomitant Medications

 Reordered and relocated language under newly created subsection headers, Permitted Medications and Prohibited Medications. Key changes include:

Permitted Medications

• #5. Use of medication to treat infusion reactions.

Section 9, Study Rules	 #6. Low-strength corticosteroids applied to a single lesion. #7. Topical tacrolimus, sirolimus or pimecrolimus applied to a single lesion. #8. Dexamethasone elixir solution for oral lesions. #9. Stable use of immunosuppressants: tacrolimus, sirolimus, pimecrolimus, methotrexate, cyclophosphamide, and dapsone. #10. One month after the final dose of SYNT001, corticosteroids may be tapered at the Investigator's discretion. Prohibited Medications #4. IV corticosteroids prior to infusion (except in subjects who received corticosteroids for treatment of a prior infusion reaction to SYNT001). #7. Vaccinations post treatment window reduced from 56 days to 28 days. Deleted corticosteroid taper instructions. Subject Withdrawal Subjects that require a significant increase in dose(s) of anti-pemphigus medications(s) for the management of their pemphigus will be encouraged to return for follow-up visits to capture safety data. Dose Escalation Stopping Rule The description of dose escalation stopping rules now reflects the new
	study design.The DEC now has the ability to reduce the dose within a cohort and
	potentially add study subjects to a given cohort.
Section 10, Evaluation of Safety	The content of this section has not changed substantially, but text has been reorganized to improve flow and ability to locate critical information in the case of a safety event.
Section 11, Statistical Considerations	 General design has been updated to mirror the protocol title. Dose selection data will be evaluated based on IgG response and PDAI score reduction. Study drug serum concentrations will be calculated by C_{max} and T_{max} for Cohorts 2, 3 and optional Cohort 4.
Section 12, Study Management	 Study Administrative Structure table has been updated with Medical Director and a new Sponsor Contact information. Informed Consent procedures have been edited to add International Council on Harmonisation Good Clinical Practice (ICH GCP) compliance language. Subject confidentiality and privacy language have been added to clarify Health Insurance Portability and Accountability Act (HIPPA) confidentiality guarantees and data protection. Audits and inspections may be performed by the sponsor to ensure validity of study data.
Global Changes	Edits and formatting changes have been made throughout to improve clarity and readability.

- Typographical and formatting corrections as well as corrections for consistency have been made.
- Renamed sections and subsections to reflect content and protocol naming conventions. Reordered language under modified or newly created subsection headers.
- Consolidated language if repeated in more than one section of protocol.
- Naming convention for sponsor changed from Syntimmune to Sponsor.
- Chronic pemphigus revised to pemphigus to indicate accepted medical terminology.
- Nomenclature for investigational product revised to study drug for consistency.
- Medical Monitoring and Sponsor contact information updated.

SYNTIMMUNE, INC. CLINICAL STUDY PROTOCOL

A Phase 1b/2, Multicenter, Open-Label, Safety, and Dose-Finding Study of SYNT001 in Subjects with Pemphigus (Vulgaris or Foliaceus)

Protocol Number: SYNT001-103

IND Number: 132727 Study Drug: SYNT001

Sponsor: Syntimmune, Inc.

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 Original Protocol:
 18 January 2017

 Amendment 1.1:
 21 March 2017

 Amendment 2.0
 12 April 2017

 Amendment 3.0
 10 October 2017

 Amendment 4.0
 08 June 2018

 Amendment 5.0
 18 September 2018

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SPONSOR SIGNATURE

I have read and approve this protocol. My signature, in conjunction with the signature of the Investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (GCP), the United States Code of Federal Regulations (CFR), and the ethical principles that have their origins in the Declaration of Helsinki.

PPD	
	19 SEPT 2018
	Date of Signature
Syntimmune Inc	

INVESTIGATOR SIGNATURE

I have read and approve this protocol. My signature, in conjunction with the signature of the Sponsor, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (GCP), the United States Code of Federal Regulations (CFR), and the ethical principles that have their origins in the Declaration of Helsinki.

Nothing in this document is intended to lim	it the authority of a physicia	n to provide emergency
medical care under applicable regulations.		

Investigator Signature	Date of Signature
Name of Investigator (please print)	

1. SYNOPSIS

Study title	A Phase 1b/2, Multicenter, Open-Label, Safety, and Dose-Finding Study of
	SYNT001 in Subjects with Pemphigus (Vulgaris or Foliaceus)
Sponsor	Syntimmune, Inc.
Protocol number	SYNT001-103
Clinical phase	Phase 1b/2
Number of study centers	Approximately 20 global study sites
Study rationale	Pemphigus is a potentially life-threatening group of rare blistering autoimmune diseases that affect the skin and mucous membranes. The exact cause is unknown, though autoantibodies are thought to play an important pathogenic role in the mucosal and cutaneous manifestations in patients with pemphigus. The prognosis of pemphigus has markedly improved over the last decades with steroid therapy. Nevertheless, mortality remains an issue (1.6% to 12% of cases) (Hsu et al., 2016; Kasperkiewicz et al., 2017; Langan et al., 2008). In these cases, death typically occurs as a consequence of treatment-related systemic infections and in a smaller proportion, as a consequence of superinfected lesions. While steroids have greatly improved patient outcomes, they are associated with serious and long-lasting side effects; therefore, their use should be limited as much as possible. Although other currently available treatments for certain autoimmune disorders, including immunosuppressants, intravenous immunoglobulin (IVIG), plasmapheresis, and anti-CD20 monoclonal antibodies (mAbs), such as rituximab, can be effective, they can be associated with significant adverse effects and delayed or non-durable responses. SYNT001 targets key mechanisms contributing to pathology in a variety of immunoglobulin G (IgG)-mediated autoimmune disorders. When administered to healthy subjects, SYNT001 has been shown to significantly decrease total IgG, as well as immune complexes with which IgG is associated. Based on these results, it is predicted that SYNT001 will also reduce the levels of pathogenic autoantibodies. This could lead to a decrease in the mucosal and cutaneous manifestations in patients with pemphigus. Moreover, the ability of SYNT001 to reduce circulating immune complexes (CICs) and the associated innate and adaptive immune responses may allow for sustained disease modification. Thus, this study is being conducted to evaluate the safety and
	immunogenicity and determine a minimally effective dose (MED) of intravenous (IV) SYNT001 in pemphigus patients.

Study objectives and endpoints	The study objectives and their correspo and exploratory) are detailed below.	nding endpoints (primary, secondary,
-	Primary Objectives	Primary Endpoints
	Safety: To evaluate the safety of IV infusions of SYNT001 at different dose levels and dosing regimens in subjects with pemphigus (vulgaris or foliaceus)	Safety: The evaluation of SYNT001 safety based on vital signs, physical examinations, electrocardiograms (ECGs), clinical safety laboratory tests, the incidence of adverse events (AEs), treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) summarized by dose and dosing regimen, severity, and relationship to study drug
	Dose Selection: To determine a MED of SYNT001 as assessed by (i) total IgG level nadir and (ii) the proportion of subjects that meet the criteria for response by Pemphigus Disease Area Index total activity score (PDAI)	Dose Selection: The determination of dose and dosing regimen of SYNT001 that achieves (i) total IgG level nadir decrease by ≥60% and ≤90% from baseline and (ii) a PDAI total activity score of ≥50% reduction from baseline to allow further clinical development in subjects with pemphigus (vulgaris or foliaceus)
	Secondary Objectives	Secondary Endpoints
	To evaluate the efficacy of doses of SYNT001 at different dose levels and dosing regimens on pharmacodynamics (PD) biomarkers	The evaluation of PD biomarkers based on absolute serum levels and percent change from baseline of total IgG, IgG subtypes (IgG1-4), immunoglobulin A (IgA), immunoglobulin M (IgM), albumin, and CIC summarized by dose, dosing regimen and visit

To determine the pharmacokinetics (PK) of SYNT001 following IV infusions at different dose levels and dosing regimens	The determination of PK parameters including half-life ($t_{1/2}$), maximum serum concentration determined directly from the concentration-time profile (C_{max}), observed time of peak serum concentration (T_{max}), area under the serum concentration-time curve from pre-dose (time ₀) to 24 hours post-dose (AUC_{0-24}), and area under the serum concentration-time curve from pre-dose (time ₀) to infinity ($AUC_{0-\infty}$), (Cohort 1); maximum serum concentration determined directly from the maximum serum concentration and corresponding T_{max} (Cohort 2) summarized by dose, dosing regimen, visit and time point
To assess the efficacy of doses of SYNT001 at different dose levels and dosing regimens on disease markers	 The assessment of pemphigus disease activity by responses on the PDAI based on absolute and percent change from baseline, summarized by dose, dosing regimen and visit The assessment of pemphigus disease activity by pathogenic antibody levels based on absolute and percent change from baseline of serum antidesmoglein 1 and 3 antibody (anti-Dsg 1 and anti-Dsg 3) levels summarized by dose, dosing regimen and visit
To measure the immunogenicity of SYNT001 administered at different dose levels and dosing regimens	The immunogenicity of SYNT001 as determined by presence of anti-SYNT001 binding antibodies and neutralizing antibodies summarized by dose, dosing regimen, visit and time point
Exploratory Objectives	Exploratory Endpoints
To explore the effect of SYNT001 at different dose levels and dosing regimens on biomarkers to understand the pathophysiology of the disease and the SYNT001 mechanisms of action	The exploration of SYNT001 mechanisms of action and effects of SYNT001 on pathophysiology summarized by dose, dosing regimen and visit as determined by:

To determine the impact of different SYNT001 dose levels and dosing regimens on the subject's use of corticosteroids to treat their	 Complement component 3 levels by nephelometry Anti-epithelial cell antibody (AECA) titers by indirect immunofluorescence Fc gamma R2A receptor (FCGR2A) single nucleotide polymorphisms (SNP) by genotyping Presence of disease and inflammatory markers by total RNA sequencing Immunophenotyping including measurements of T cells, monocytes, natural killer (NK) cells and B cells by flow cytometry Urine IgG levels to explore SYNT001 distribution and elimination (Cohort 1 only) Exploratory biomarkers to investigate immune response associated with pemphigus The evaluation of corticosteroid use during the study will be summarized by dose, dosing regimen and visit
pemphigus (vulgaris or foliaceus) To assess the impact of SYNT001 on the subject's health-related quality of life (HR-QoL) at different dose levels and dosing regimens	The assessment of SYNT001 impact on subject's health-related quality of life (HR-QoL) by responses to the Autoimmune Bullous Diseases Quality of Life (ABQoL) questionnaire and Skindex-29 scores summarized by dose, dosing regimen and visit
To assess the effect of SYNT001 on the appearance of skin and mucosal lesions at different dose levels and dosing regimens	The qualitative assessment of changes in appearance of skin and mucosal lesions as determined by photography presented by dose, dosing regimen and visit
To quantify the amount of SYNT001 in skin (skin biopsies optional)	The determination of SYNT001 levels in skin biopsies across timepoints (skin biopsies optional) (Cohort 1 only)

Study design

This is a multicenter, open-label safety study to determine the dose regimen of SYNT001 administered IV in subjects with pemphigus (vulgaris or foliaceus).

Up to 8 subjects with a diagnosis of pemphigus (vulgaris or foliaceus) will receive SYNT001 10 mg/kg weekly x 5 doses (Cohort 1).

Up to 12 subjects with a diagnosis of pemphigus (vulgaris or foliaceus) will receive SYNT001 30 mg/kg weekly x 3 doses (Loading), followed by SYNT001 10 mg/kg every other week x 5 doses (Maintenance) (Cohort 2).

Subjects in both cohorts will complete the following periods of assessment: Screening, Treatment, and Follow-Up. For Cohort 1 details of the dosing schedule and assessments, see Table 2. For Cohort 2 details, see Table 3.

The Dose Escalation Committee (DEC) will consist of the Medical Monitor, an Independent Clinical Expert and the Sponsor Medical Lead. The DEC may request that Investigators, other experts, or members within their organization participate in the review. Additional information on the DEC's responsibilities is provided in Section 9.5 and the DEC Charter.

An overview of the study cohorts is provided in Table 1 and Figure 1 shows a schematic of the study design.

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Table 1.	Cohort Overvie	W

Cohort No.	No. of Subjects	SYNT001 Dose	No. of Doses	Frequency of Doses
1 ^a	Up to 8	10 mg/kg	5	Weekly
2 ^b	Up to 12	Loading: 30 mg/kg ^c	3°	Weekly ^c
		Maintenance: 10 mg/kg ^c	5°	Every other week ^{c, d}

- a. No more than 3 subjects with pemphigus foliaceus may be enrolled
- b. Two or fewer subjects with pemphigus foliaceus may be enrolled
- c. The dose, number of doses, and frequency of doses in Cohort 2 will be confirmed based on review of safety and PD evaluations, including but not limited to, dose-limiting toxicities, AEs, TEAEs, SAEs, and total IgG levels. Following Sponsor review of emerging safety, PD and efficacy data, the Loading dose may be reduced to 20 or 10 mg/kg weekly and/or the Maintenance dose may be increased to 20 or 30 mg/kg every other week and/or dose frequency may be increased to weekly.
- d. Ongoing safety and PD evaluations may result in modification of the dose and dosing regimen in Cohort 2. See APPENDIX 5 for the corresponding visit schedule.

Subjects will be enrolled at staggered intervals to facilitate adequate safety evaluation before dosing of subsequent subjects .

At 24-hour and 7-day intervals described below, all available safety data (including but not limited to dose limiting toxicities [DLTs], AEs, TEAEs, SAEs and PD (including but not limited to total IgG levels), will be reviewed.

Safety Review of 24-hour Data for Cohorts 1 and 2, Subject 1

• The first 2 subjects in each cohort will be dosed at least 24 hours apart. A DEC review of the 24-hour safety data for the first subject in Cohort 1 will be performed to ensure that there are no overt safety concerns

	before dosing the second subject. The Sponsor Medical Lead and Medical Monitor will conduct the 24-hour safety data review for the first subject in Cohort 2.
	Safety Review of 7-day Data for Cohorts 1 and 2, Subjects 1 and 2
	• The 7-day safety data for the first 2 subjects in Cohort 1 will be reviewed by the DEC prior to dosing the remaining subjects in the cohort. The Sponsor Medical Lead and Medical Monitor will conduct the 7-day safety data review in Cohort 2.
	The 24-hour and 7-day reviews will consider seriousness and severity of AEs/TEAEs/SAEs and relatedness to study drug, vital sign assessments, physical examinations, and clinical laboratory testing.
	Safety data (including but not limited to DLTs, AEs, TEAEs, SAEs), and PD data (including but not limited to IgG levels) will be reviewed on an ongoing basis by the Medical Monitor and the Sponsor Medical Lead. In addition, at any point the DEC may initiate a review of all cumulative data if requested by a DEC member.
	 If a DLT occurs, dosing will be halted within that cohort and dose-escalation will not occur. NOTE: DLTs will be defined generally as severe (Grade 3) AEs occurring in ≥2 subjects that are determined to be clinically significant and considered related to study drug. If any subject at any time during the study experiences a life-threatening AE (Grade 4) that is considered related to study drug, further dosing in all enrolled subjects will be suspended. At any time during the study, the study or any ongoing study cohort may be discontinued if the Sponsor Medical Lead determines that further drug exposure would pose an undue risk to subjects.
	Dosing for any individual subject will be discontinued (ie, no further administration of SYNT001) if the subject experiences any study drug-related SAE or any study drug-related non-serious AE that, in the judgement of the Investigator (following consultation with the Medical Monitor, if desired), or in the judgement of the Sponsor Medical Lead, suggests that it could be unsafe to administer further study drug to that subject.
Number of subjects	Up to 20 subjects are planned; up to 8 subjects in Cohort 1 and up to 12 subjects in Cohort 2. Subjects who withdraw for any reason other than an AE may be replaced.
Study population	Male or female subjects 18 years of age and older with a confirmed diagnosis of pemphigus (vulgaris or foliaceus)
Diagnosis and main	Inclusion criteria:
entry criteria	Subjects must meet the following criteria to be eligible for the study:
	 Willing and able to read, understand, and sign an informed consent form. Male or female ≥18 years of age at the time of screening. Documented diagnosis of pemphigus vulgaris or foliaceus based on all 3 of the following criteria:

- a. Documented clinical history consistent with pemphigus vulgaris or foliaceus (clinical presentation defined as mucosal and/or skin lesions).
- b. Presence of Anti-Dsg 1 or 3 antibodies above the upper limit of normal (ULN).
- c. History of at least one positive tissue-based test (eg, biopsy, direct immunofluorescence [DIF]).
- 4. Active disease defined as lesions lasting >2 weeks, and 3 active lesions in skin or mucosa or 2 active lesions with at least one being a skin lesion >1 cm diameter:
 - a. If treated with rituximab or other anti-CD20 mAb, last dose >9 months prior to screening.
 - b. If being treated with other immunosuppressants (ie, azathioprine, mycophenolate mofetil, methotrexate, dapsone, cyclosporine, tacrolimus, sirolimus, or low-dose cyclophosphamide [≤100 mg/day]), dose must be stable, defined as <25% change in dose, for 4 weeks prior to screening.
 - c. On stable dose of corticosteroids, defined as ≤1 mg/kg of prednisone or equivalent and may not be increased by more than 50% in the 2 weeks prior to screening.
 - d. Allowed topical therapies for pemphigus lesions upon entering the study include petroleum jelly or Aquaphor® for the skin or chlorhexidine for the mouth.
 - e. Stable use of topical low strength hydrocortisone (≤1%), tacrolimus, sirolimus, or pimecrolimus for lesions contributing <10% of the PDAI total activity score for the 4 weeks prior to screening is allowed. Stable use of dexamethasone elixir solution (swish and spit only) for oral lesions for the 4 weeks prior to screening is allowed.
 - f. If not on regular corticosteroids, no pulse corticosteroids are allowed in the 2 weeks prior to screening.
- 5. Body mass index (BMI) $> 18.5 \text{ kg/m}^2$.
- 6. Has a negative pregnancy test documented prior to the first dose of study drug (for women of childbearing potential).
- 7. Females of childbearing potential must agree to be abstinent or else use any two of the following medically acceptable forms of contraception (<1% per year failure rate) from the screening period through the final study visit: oral contraceptive, condom with or without spermicidal jelly, diaphragm or cervical cap with spermicidal jelly, or intrauterine device (IUD). A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception.
- 8. Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months do not require contraception during the study.
- 9. Males with female partners of childbearing potential, including males who are surgically sterile (post vasectomy), must agree to be abstinent or else use a medically acceptable form of contraception from the screening period through the final study visit.
- 10. A PDAI total activity score of >4 at screening.

Exclusion criteria:

Subjects meeting any of the following criteria are ineligible for the study:

- 1. Subject unable or unwilling to comply with the protocol.
- 2. Active non-hematologic malignancy or history of non-hematologic malignancy in the 3 years prior to screening (exclusive of non-melanoma skin cancer and cervical cancer in situ).
- 3. Positive for human immunodeficiency virus (HIV) or hepatitis C antibody.
- 4. Positive for hepatitis B surface antigen.
- 5. Active infection or history of recurrent infections.
- 6. IVIG treatment within 30 days of screening.
- 7. Received any cytotoxic (other than azathioprine) or any non-anti-CD20 mAb therapy in the 3 months prior to screening.
- 8. Any exposure to an investigational drug or device within the 30 days prior to screening.
- 9. Plasmapheresis or immunoadsorption within 30 days of screening.
- 10. Cellular therapy, including chimeric antigen receptor and T-cell (CAR-T), at any time prior to screening.
- 11. Use of any systemic or topical immunosuppressive drugs within 3 months of screening not including those allowed by the inclusion criteria.
- 12. Serum total IgG <600 mg/dL at screening.
- 13. Subject has any current medical condition that, in the opinion of the Investigator, may compromise their safety or compliance, preclude successful conduct of the study, or interfere with interpretation of the results (eg, a significant pre-existing illness or other major comorbidity that the Investigator considers may confound the interpretation of the study results).
- 14. Any vaccination within 2 weeks of screening.

Study drug, dosage, and administration

Study drug: SYNT001

Dosages:

Cohort 1: 10 mg/kg x 5 weekly doses

Cohort 2: 30 mg/kg x 3 weekly doses (Loading) followed by 10 mg/kg every other week x 5 doses (Maintenance).

The dose, number of doses, and frequency of doses in Cohort 2 will be confirmed based on ongoing review of safety and PD evaluations, including but not limited to, DLTs, AEs, TEAEs, SAEs, and total IgG levels. Following Sponsor review of emerging safety, tolerability, PD and efficacy data, the Loading dose may be reduced to 20 or 10 mg/kg weekly and/or the Maintenance dose may be increased to 20 or 30 mg/kg every other week and/or dose frequency may be increased to weekly.

Product presentation and preparation:

SYNT001 provided as a liquid at a nominal concentration of 50 mg/mL. SYNT001 is diluted in dextrose 5% in water (D5W) to prepare the solution for infusion.

Route of administration: IV in 250 mL over 1 hour \pm 15 minutes Investigators may adjust the duration of the infusion if needed to improve tolerability.

Control dos ond	Not applicable										
Control, dose, and route of	Not applicab	ie									
administration											
Duration of subject	The duration	of subject pa	rticipation for	r each cohort	is as follows	s:					
participation	Cohort Screening Treatment Follow-up Maximum Tota										
				_	Days	Weeks					
	1	≤14 days	28 days	84 days	126 days	18 weeks					
	2	≤14 days	84 days	56 days	154 days	22 weeks					
		l	l		-1						
Permitted and prohibited concomitant treatments	All pemphigus treatments a subject receives within at least 3 months prior to enrollment and all other treatments a subject receives within 14 days prior to enrollment through the end of the study will be documented. Permitted Medications										
	Concomitant	medication a	and treatment	for co-existing	ng conditions	s, including					
			permitted if no								
	 Topical 1 Topical 1 Concome experien Medication acetamin (eg, raningle leg) Topical 1 Low-stressingle leg Topical 1 Contributes Dexamentation Stable region Stable region cyclophology 	or systemic traidocaine for the docaine for the docaine for the docaine for the docaine for potent headache: the docaine, IV hybridine, famotion contributed acrolimus, sitting <10% of the docaine elixing the docaine of the docaine, mycophorine, tacrolimus osphamide (\lequip esphamide (\lequip esphamide))	e study. ial infusion-re ial infusion-re ial infusion-re ial infusion-re ial infusion-re ial infusion, diphe dine). corticosteroid ing <10% of rolimus or pir the PDAI tota solution for c ipation (swish following systemolate mofet ius, sirolimus 100 mg/day).	oral candidia relief as nee cally indicate elated reaction may recommenhydramine s (eg, hydrocothe PDAI tothe mecrolimus and activity seconal lesions it in and spit only temic immunial, low-dose in conticostero	sis. ded. ed for any AF ed for any AF ens (IRRs), in nend prophyl , histamine ₂ (cortisone ≤1% al activity sc pplied to a si ore. To dose remain ly). hosuppressan methotrexate ids, or low defined.	Es the subject cluding post-actic use of (H ₂) blockers 6) applied to a ore. ngle lesion as stable ats: , dapsone, ose oral					
	at the Investi	Fourteen days after the final dose of SYNT001, corticosteroids may be tapered at the Investigator's discretion.									
	Prohibited I										
		llowing medi ove as permitt		ot be permit	ted during the	e study unless					
	Monoclo Any topi are listed IV cortice corticost	onal antibodie cal or system l as permitted costeroids prio	or to infusion atment of a pr	tudy drug opressive dru (except in su	bjects who re	eceived					

6. Vaccinations within 2 weeks of screening through 28 days following final dose of study drug

Corticosteroids

Before enrollment

The dose of corticosteroids taken for pemphigus or any other condition prior to screening must be at a dose ≤ 1 mg/kg and the dose level must have not increased in dose level by more than 50% in the 2 weeks prior to screening. No pulse dosing of steroids is permitted in the 2 weeks prior to screening.

From screening until 2 weeks after the last dose of SYNT001

The dose of corticosteroids taken for pemphigus or any other condition should remain stable (<10% change in dose level) from screening until 2 weeks after the last dose of SYNT001. Corticosteroids should neither be started nor discontinued during this period with the exception of subjects who experience an IRR that requires corticosteroids as part of the management of the IRR. Such subjects may receive corticosteroids prophylactically prior to subsequent SYNT001 infusions at the discretion of the Investigator.

From 2 weeks after the last dose of SYNT001 until end of study participation

At the discretion of the Investigator, but only after at least 2 weeks beyond the last dose of SYNT001, a slow corticosteroid taper may be started as per the following suggested schedule:

• If on >30 mg of prednisone per day, decrease by no more than 10 mg every two weeks until a final dose.

If per the Investigator's judgement, the subject would benefit from a change to the pemphigus treatment beyond the allowed steroid taper, this will be considered on a case-by-case basis in consultation with the Sponsor.

Statistical considerations

Three populations will be employed in the analysis of study data:

- The Safety population will consist of all subjects who have received at least one dose of study drug.
- The PD population will consist of all subjects who receive at least one dose of study drug and have post-dose PD data available.
- The PK population will consist of all subjects who receive at least one dose of study drug and have post-dose PK data available.

Primary safety analyses will be performed on the safety population. Demographics, subject disposition, screening, and baseline characteristics will be summarized for the Safety, PD and PK populations, where appropriate.

Sample size

Formal sample size calculations were not performed. The number of subjects was chosen based on feasibility and was considered sufficient to meet the study objectives.

Criteria for evaluation

Baseline analysis

Baseline characteristics to include medical history, physical examination, vital signs, and ECG will be summarized using descriptive statistics by dose, dose regimen, and visit.

Safety analysis

The evaluation of SYNT001 based on vital signs, physical examination, ECGs, clinical safety laboratory tests, the incidence of AEs, TEAEs, and SAEs summarized by dose and dose regimen, severity, and relationship to study drug.

Dose-finding analysis

The evaluation of SYNT001 based on total IgG levels and responses on the PDAI total activity score from baseline will be summarized using descriptive statistics by dose and dose regimen, visit and time point, as applicable.

Statistical methodology

Treatment-emergent AEs (TEAEs) will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA®; Version 19 or higher) System Organ Class (SOC) and preferred term, classified from verbatim terms. The incidence and percentage of subjects with at least one occurrence of a preferred term will be included, using the most severe grade. The number of events per preferred term will also be summarized. Causality (relationship to study drug [related/not related]) will be summarized separately.

TEAEs, SAEs, and AEs leading to withdrawal, dose modification, or treatment discontinuation will be listed by subject and dose using SOC and preferred terms. Duration of AEs will be determined and included in listings, along with action taken and outcome.

Laboratory results will be summarized by time point, dose, and dose regimen. The incidence of laboratory abnormalities will be summarized. The worst onstudy grade after the first dose of study drug will be summarized. Results for variables that are not coded will be presented in the listings as below, within, or above the normal limits of the central laboratory. Vital sign measurements and change from baseline will be summarized at each scheduled time point using descriptive statistics. PD/PK results will be summarized by dose and dosing regimen. Descriptive statistics of PD/PK parameters for SYNT001 will include mean, standard deviation (SD), coefficient of variation (CV), median, minimum, and maximum.

Immunogenicity results will be summarized by cohort, visit and time point. Descriptive statistics will include mean, SD, CV, median, minimum, and maximum.

Disease activity marker results will be summarized by dose, dose regimen, and visit. Descriptive statistics will include mean, SD, median, minimum, and maximum.

PDAI results will be summarized by score (total activity score, total damage score), cohort, and visit. Descriptive statistics will include absolute change from baseline and percent change from baseline.

Additional statistical analyses may be performed.

Figure 1. Cohort Enrollment

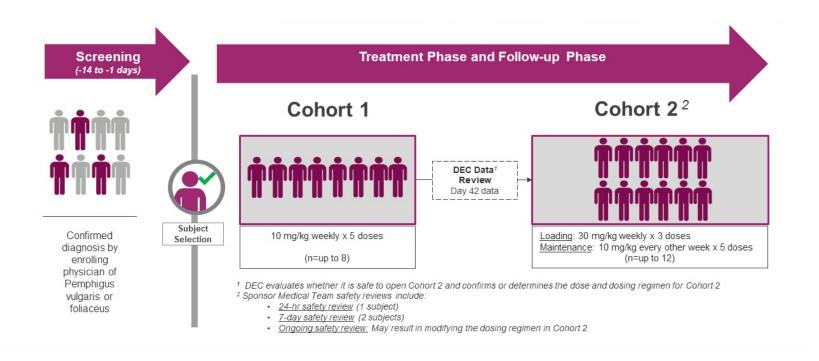


Table 2. Study Assessments for Cohort 1

	Screening							Tre	atment	Period							Follo	w-Up
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Time point (study day)	-14 to -1	0	1	2	5 ^p	7	12 ^p	14	19 ^p	21	28	29	30	33	42	56	84	112 or
			(±1 h)	(±2 h)	(±4 h)	(±6 h)	(±6 h)	(±6 h)	(±6 h)	(±6 h)	(±6 h)	(±1 h)	(±2 h)	(±4 h)	(±3 d)	(±5 d)	(±5 d)	ET (±5 d)
Informed consent	X																	
Demographics/medical history	X																	
Inclusion/exclusion	X																	
Physical examination ^a	X	X				X		X		X	X				X	X	X	X
Vital signs ^b	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pulse oximetry ^c		X				X		X		X	X							
Clinical safety labs ^d	X	X				X		X		X	X			X	X	X	X	X
Pregnancy test ^e	X	X														X		X
Hepatitis and HIV screen	X																	
12-lead ECG ^f	X	X					X				X					X		
Tetanus and VZV antibodies ^g		X														X	X	X
PDAI		X				X		X		X	X			X	X	X	X	X
PK sampling ^h		X	X	X	X						X	X	X	X				
Immunogenicity ⁱ		X						X			X					X	X	X
Study drug administration ^j		X				X		X		X	X							
Immunoglobulins (IgG, IgA, IgM) and IgG subtypes (IgG1-4) ^k	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Xq
CIC		X			X	X	X	X	X	X	X			X	X	X	X	X
Anti-Dsg (1 and 3) antibody titers	X	X				X		X						X		X	X	X
C3 and AECA ¹		X						X						X		X	X	X
FCGR2A by buccal swab ^m		X																
RNAseq		X						X						X		X	X	X
Urine IgG		X						X						X		X	X	X
Immunophenotyping ⁿ		X									X					X		
Exploratory pemphigus immune response biomarkers		X			X	X	X	X	X	X	X			X	X	X	X	X
Optional skin biopsy		X	X	X				X						X		X	X	
Photography ^o		X												X		X	X	X
Adverse events					To be co	ollected	from the	e date th	at the IC	F is sig	ned thro	ugh the	last stud	ly visit	•	•	•	
Concomitant medications								ithin 14 c										

Abbreviations: CIC = circulating immune complexes; d = days; ECG = electrocardiogram; ET = early termination; h = hour(s); HIV = human immunodeficiency virus; ICF = informed consent form; PDAI = Pemphigus Disease Area Index; PK = pharmacokinetic; VZV = varicella zoster virus.

- a. Complete physical examination, including weight, to be performed. Height and BMI will be additional assessments conducted at screening.
- b. **Vital sign** measurements (sitting blood pressure, heart rate, respiratory rate, and oral temperature) to be obtained after 5 minutes of seated rest. Any abnormal measurements are to be repeated after 5 minutes of rest. On Days 0, 7, 14, 21, and 28, vital sign measurements will be collected immediately prior to the infusion; 15, 30, and 45 minutes after the start of the infusion; at completion of the infusion; and 30 minutes, 1 hour, and 2 hours following completion of the infusion.
- c. **Pulse oximetry:** On Days 0, 7, 14, 21, and 28, pulse oximetry to be measured immediately prior to the infusion; 15, 30, and 45 minutes after the start of the infusion; at completion of the infusion; and 30 minutes, 1 hour and 2 hours following completion of the infusion.
- d. Clinical safety labs: hematology, clinical chemistry, and urinalysis (see Section 7.5 for a complete list). Full clinical safety laboratory draws will be collected at screening and on Days 0, 7, 14, 21, 28, 33, 42, 56, 84, and 112.
- e. **Pregnancy test (women of childbearing potential only):** To be performed at time of screening, prior to first dose of SYNT001 on Day 0, and on Days 56 and 112. Urine or serum test is acceptable; however, positive urine tests must be confirmed with serum testing.
- f. Digital 12-lead ECG to be obtained in triplicate at least 1 to 2 minutes apart and after 5 minutes of rest in a supine position. See Section 7.6 for additional information. On Days 0 and 28 to be obtained 5 minutes after the completion of infusion. Day 12 ECG will be collected only if the visit is conducted at the study site.
- g. **Serology**: Testing at Day 56 will not be done for any subject whose baseline titer is below the level of detection. If the Day 56 results are greater than 30% below the baseline value, or if the subject falls below the level of detection, the subject will be re-tested at Day 84; if still below the baseline value (or level of detection), the subject will be re-tested at Day 112. Any subject whose baseline value for tetanus or VZV was above the detectable level at baseline, and is not within 30% of the baseline value or is below the detectable level by Day 112, will be referred to their primary care physician for further management. See Section 7.5.3 for additional information.
- h. **PK**: Starting on Days 0 and 28, serum samples will be collected just prior to the start of study drug infusion (pre-dose), and at 5 minutes and 2, 4, 6, 24, and 48 hours after the end-of-study drug infusion. Additional samples will be collected on Days 5 and 33. See Section 7.5.4 for additional information.
- Immunogenicity: Samples will be collected pre-dose when collected on dosing days. Samples will be collected on Days 0, 14, 28, 56, 84 and 112. See Section 7.5.6 for additional information.
- j. Prior to **study drug infusion**, SYNT001 drug product is to be diluted in dextrose 5% in water (D5W) to a total volume of 250 mL and administered intravenously over 1 hour using a 0.2-micron inline filter. See Section 4 and Section 7.8 for additional information.
- k. Immunoglobulins (IgG, IgA, IgM) and IgG subtypes (IgG1-4): Collected for measurements of IgG, IgG subtypes (IgG1-4), IgA, IgM at every visit. On Days 0, 7, 14, 21, and 28, samples are collected prior to infusion of study drug. See Section 7.5.5 for additional information.
- 1. **Exploratory pharmacodynamic samples (C3 and AECA):** Collected pre-dose when collected on dosing days. See Section 7.5.5 for complete information.
- m. Buccal samples to be collected and stored; pending review of clinical and pharmacodynamics assessments.
- n. Immunophenotyping by flow cytometry for measurement of CD3+CD4+ T, CD3+CD8+ T, monocytes, NK cells and B cells.
- o. Photographs of active lesions taken prior to first dose on Day 0. Follow-up photographs will be taken at Days 33, 56, 84 and 112. Subjects who begin a steroid taper will have additional photographs taken at the clinic visit during which the decision to begin the taper is made.
- p. Visit Days 5, 12, and 19 may be conducted via at-home nurse in lieu of a subject visit to the study site.
- q. Subjects will return to the clinic on Days 84 and 112 for follow-up visits. Subjects whose total IgG is not within 30% of their Day 0 baseline value and not above 500 mg/dL at the Day 112 visit will be referred for further management.

Table 3. Study Assessment for Cohort 2

	Screening	Screening Loading				Maintenance				Follow-Up		
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12
Time Point (Study Day)	-14 to -1	0 Baseline	7 (±1 d)	14 (±1 d)	28 (±3 d)	42 (±3 d)	56 (±3 d)	70 (±3 d)	84 (±3 d)	91 (±5 d) or ET visit	112 (±5 d)	140 (±5 d) EOS
Informed consent	X											
Demographics/medical history	X											
Inclusion/exclusion	X											
Physical examination ^a	X	X	X	X	X	X	X	X	X	X		X
Vital signs ^b	X	X	X	X	X	X	X	X	X	X	X	X
Pulse oximetry ^c		X	X	X	X	X	X	X	X			
Clinical safety labs ^d	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test ^e	X	X			X					X		X
Hepatitis and HIV screen	X											
12-lead ECG ^f	X	X		X	X					X		X
Tetanus and VZV antibodies ^g		X			X					X		X
PDAI ^h	X	X	X	X	X	X	X	X	X	X	X	X
PK sampling ⁱ		X	X	X	X				X			
Immunogenicity ^j	X	X	X	X	X	X	X	X	X	X	X	X
Study drug administration ^k		X	X	X	X	X	X	X	X			
Immunoglobulins (IgG, IgA, IgM) and IgG subtypes (IgG1-4) ¹	X	X	X	X	X	X	X	X	X	X	X	X^q
CIC		X	X	X	X	X	X	X	X	X	X	X
Anti-Dsg (1 and 3) antibody titers	X	X	X	X	X	X	X	X	X	X	X	X
C3 and AECA ^m	X	X	X	X	X	X	X	X	X	X	X	X
FCGR2A by buccal swab ⁿ		X										
RNA sequencing		X			X					X		
Immunophenotyping ^o		X			X					X		
Exploratory pemphigus immune response biomarkers		X	X	X	X	X	X	X	X	X	X	X
Photography ^p		X	X	X	X	X	X	X	X	X	X	X
HR-QoL assessments		X			X					X		X

Adverse events	To be collected from the date that the ICF is signed through the last study visit
Concomitant medications	To be collected from within 14 days prior to Day 0 through the last study visit

Abbreviations: CIC = circulating immune complexes; d = day(s); ECG = electrocardiogram; EOS = end of study; ET= early termination; FcGR2a= Fc gamma R2a receptor; HIV = human immunodeficiency virus; HR-QoL = health-related quality of life; ICF = informed consent form; Ig = immunoglobulin; PDAI = Pemphigus Disease Area Index; PK = pharmacokinetic; VZV = varicella-zoster virus

- a. Complete physical examination, including weight, to be performed. Height and body mass index will be additional assessments conducted at screening only.
- b. **Vital sign** measurements (sitting blood pressure, heart rate, respiratory rate, and oral temperature) to be obtained after 5 minutes of seated rest. Any abnormal measurements are to be repeated after 5 minutes of rest. Vital sign measurements will be taken on all study visits. On dosing days, vital sign measurements will be collected immediately prior to the infusion; 15, 30, and 45 minutes after the start of the infusion; at completion of the infusion; and 30 minutes, 1 hour and 2 hours following completion of the infusion.
- c. **Pulse oximetry**: On dosing days, pulse oximetry to be measured immediately prior to the infusion; 15, 30, and 45 minutes after the start of the infusion; at completion of the infusion; and 30 minutes, 1 hour, and 2 hours following completion of the infusion.
- d. Clinical safety labs: hematology, clinical chemistry, and urinalysis. See Section 7.5 for a complete list. Full clinical safety lab draws will be collected at screening and at all study visits prior to infusion if applicable.
- e. **Pregnancy test (women of childbearing potential only):** To be performed at time of screening and prior to dose on dosing days if applicable. Urine or serum test is acceptable; however, positive urine tests must be confirmed with serum testing.
- f. Digital 12-lead ECG to be obtained after 5 minutes of rest in the supine position and in triplicate approximately 1 minute apart. See Section 7.6 for additional information. On days of treatment, to be obtained approximately 5 minutes after the completion of infusion.
- g. **Serology:** Any subject whose baseline value for tetanus or VZV was above the protective level at baseline and is not within 30% of the baseline value or is below the protective level by End of Follow-up, will be referred to their primary care physician for further management. See Section 7.5.3 for additional information.
- h. PDAI will be administered at screening. Subject eligibility requires a PDAI total activity score >4. Thereafter, assuming eligibility, the PDAI will be administered during Treatment Period and Follow-up Period. See Section 7.7 for additional information.
- i. **PK:** Starting on dosing days, serum samples will be collected just prior to the start of study drug infusion (pre-dose) and at 5 minutes, 1 and 2 hours after the end of study drug infusion. See Section 7.5.4 for additional information.
- j. Immunogenicity: Samples will be collected pre-dose when collected on dosing days. See Section 7.5.6 for additional information
- k. Prior to **study drug infusion**, SYNT001 drug product is to be diluted in dextrose 5% in water to a total volume of 250 mL and administered intravenously over 1 hour ±15 minutes using a 0.2-micron, inline filter. See Section 4 for additional information.
- 1. Immunoglobulins (IgG, IgA, IgM) and IgG subtypes (IgG 1-4): Collected for measurements of IgG, IgG subtypes (IgG1-4), IgA, and IgM at every visit. On dosing days, samples are collected prior to infusion of study drug. See Section 7.5.5 for additional information.
- m. Exploratory pharmacodynamic samples (C3 and AECA): Collected pre-dose when collected on dosing days. See Section 7.5.5 for complete information.
- n. Buccal samples to be collected pre-dose.
- o. **Immunophenotyping** by flow cytometry for measurement of CD3⁺CD4⁺ T, CD3⁺CD8⁺ T, monocytes, natural killer (NK) cells, and B cells. Collect samples pre-dose on dosing days.
- p. Photographs of all active lesions taken pre-dose on dosing days. Subjects who begin a steroid taper will have additional photographs taken at the clinic visit during which the decision to begin the taper is made.
- q. Subjects whose total IgG is not within 30% of their Day 0 baseline value and not above 500 mg/dL at the Day 140 visit will be referred for further management.

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LIST OF ABBREVIATIONS

ABQoL Autoimmune Bullous Disease Quality of Life

ADA anti-drug antibodies

AE adverse event

AECA Anti-epithelial cell antibody ALT alanine aminotransferase AST aspartate aminotransferase

AUC₀₋₂₄ area under the serum concentration-time curve from pre-dose (time₀) to 24 hours post-

dose

AUC_{0-∞} area under the serum concentration-time curve from pre-dose (time₀) to infinity

BLQ below the limit of quantification

BMI body mass index BUN blood urea nitrogen

C1q complement component 1q C3 complement component 3

CAR-T chimeric antigen receptor and T-cell

CFR Code of Federal Regulations
CIC circulating immune complexes

C_{max} maximum serum concentration determined directly from the concentration-time

profile

CRO contract research organization

CV coefficient of variation
D5W dextrose 5% in water
DEC Dose Escalation Committee
DIF direct immunofluorescence
DLT dose-limiting toxicity
DNA deoxyribonucleic acid

dsDNA double-stranded deoxyribonucleic acid

Dsg desmoglein

ECG electrocardiogram

eCRF electronic case report form EDC electronic data capture

eGFR estimated glomerular filtration rate

ET early termination

FCGR2A Fc gamma R2a receptor FcRn neonatal Fc receptor

FDA Food and Drug Administration

GCP Good Clinical Practice
GLP Good Laboratory Practice

H₂ histamine₂

HBV hepatitis B virus HCV hepatitis C virus

HIPAA Health Insurance Portability and Accountability Act

HIV human immunodeficiency virus
HR-QoL health-related quality of life
IB Investigator's Brochure
IC immune complex

ICF Informed Consent Form

ICH International Council for Harmonisation of Technical Requirements for

Pharmaceuticals for Human Use

IgA immunoglobulin A IgG immunoglobulin G IgG1-4 immunoglobulin G1-G4 IgM immunoglobulin M **IND** investigational new drug IRB institutional review board **IRR** infusion-related reaction **IUD** Intrauterine device

IV intravenous

IVIG intravenous immunoglobulin

LDH lactate dehydrogenase
LLN lower limit of normal
mAb monoclonal antibody
MED minimum effective dose

MedDRA Medical Dictionary for Regulatory Activities

NCI CTCAE National Cancer Institute Common Terminology Criteria for Adverse Events

NHP nonhuman primate NK natural killer

NOAEL no observed adverse effect level

PD pharmacodynamics

PDAI Pemphigus Disease Area Index

PK pharmacokinetic

QTcF corrected QT interval using Fridericia's formula

RNA ribonucleic acid
RNAseq RNA sequencing
SAE serious adverse event
SAP statistical analysis plan
SAS Statistical Analysis System

SD standard deviation

SNP single nucleotide polymorphism

SOC system organ class

SYNT001 a humanized, affinity matured IgG4-kappa monoclonal antibody

 $t_{1/2}$ Half-life

TEAE treatment-emergent adverse event

 T_{max} observed time to reach peak plasma concentration

ULN upper limit of normal
US United States of America
VZV varicella zoster virus

WHO World Health Organization

WHO-DD World Health Organization Drug Dictionary

2. BACKGROUND AND RATIONALE

SYNT001, a humanized, affinity-matured IgG4-kappa monoclonal antibody (mAb), blocks immunoglobulin G (IgG) and IgG immune complex (IC) interactions with the neonatal crystallizable fragment receptor (FcRn), and inhibits the varied roles of FcRn in the immune response.

Through specific and high affinity blockade of FcRn, SYNT001 has been shown to increase the catabolism of IgG and IgG IC in healthy volunteers and is predicted to block the ability of IgG IC to activate intracellular signaling events associated with binding to FcRn. This predicts that SYNT001 will also accelerate degradation of endogenous circulating IgG autoantibodies and IgG-IC specifically involved in the pathogenesis of autoimmunity. Blocking FcRn interactions with IgG ICs further predicts that SYNT001 will have consequences for innate and adaptive cellular immunity. In the first instance, blocking multimeric IgG IC interactions with FcRn within antigen-presenting cells should result in inhibition of IC-mediated inflammatory cytokine production and release by these cells. In addition, as FcRn determines the intracellular itinerary of IgG ICs within and among compartments important in cellular immunity, it is further anticipated that SYNT001 will block antigen processing and presentation of antigens contained within ICs that would otherwise lead to CD8⁺ and CD4⁺ T cell activation. Thus, SYNT001 is expected to specifically target immune functions associated with IgG and IC that are involved in certain IgG-mediated autoimmune conditions.

SYNT001 targets key mechanisms contributing to pathology in a variety of IgG-mediated autoimmune disorders.

While current treatments for certain autoimmune disorders, including chronic steroids, immunosuppressants, intravenous immunoglobulin (IVIG), plasmapheresis, and anti-CD20 mAbs, such as rituximab, can be effective, they are associated with significant adverse effects, and delayed or non-durable responses.

Pemphigus is a rare group of blistering autoimmune diseases that affect the skin and mucous membranes. Autoantibodies are thought to play an important pathogenic role in the mucosal and cutaneous manifestations in patients with pemphigus. Administration of SYNT001 significantly decreases total IgG levels, including a corresponding decrease in the levels of the pathogenic autoantibodies. This may lead to a decrease in the mucosal and cutaneous manifestations in patients with pemphigus. Moreover, the ability of SYNT001 to reduce IgG ICs and the associated innate and adaptive immune responses may allow for further sustained disease modification.

2.1 Study Rationale

This study is being conducted to evaluate the safety, dose, pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity of intravenous (IV) SYNT001 as well as its effects on pemphigus disease activity markers.

2.2 Selection of Doses in this Study

The initial SYNT001 dose levels for study SYNT001-103 were selected following careful review of the safety, tolerability, and PD effect on total IgG levels studied in non-human primates (NHP) and healthy male subjects.

Four repeat-dose toxicology studies in cynomolgus monkeys examined 2 to 14 repeat weekly IV doses 5 to 100 mg/kg SYNT001 with up to a 4-week follow-up. There was one death in the 14-week study attributed to an immune-evoked infusion reaction, which correlated with the development of anti-drug antibodies (ADAs), circulating immune complexes, circulating complement depletion, and deposition of immune complexes containing SYTN001 and complement in tissues. Across studies, clinical signs were limited to reports of transient emesis/vomitus following dosing and facial flushing and periocular swelling observed in the 5-week study after the third dose coincident with the first appearance of ADAs. With the exception of emesis/vomitus, these clinical signs were effectively controlled with diphenhydramine pretreatment in the 5-week study and the subsequent 14-week study. There were no adverse SYNT001-related changes in weight gain, clinical chemistry, gross or histo-pathology. The No Observed Adverse Effect Level (NOAEL) was the highest dose tested in all 4 studies and the overall NOAEL following repeat weekly exposure to STYNT001 of up to 14 doses in cynomolgus monkeys was 100 mg/kg.

The safety, tolerability, and PD effect on total IgG levels in study SYNT-101—a Phase 1a study that assessed single ascending doses of SYNT001 in healthy male subjects—were also reviewed. In study SYNT-101, the doses of SYNT001 up to and including 30 mg/kg were well tolerated. There were no dose-limiting toxicities, serious adverse events (SAEs), or any other safety concerns. No adverse events (AEs) were observed in the 1 and 3 mg/kg dose cohorts. Headache was the most commonly reported treatment-emergent adverse event (TEAE), occurring in 8 of 11 subjects treated with 10 or 30 mg/kg SYNT001. One headache in the 10 mg/kg cohort was moderate (Grade 2) in severity; all other headaches were mild (Grade 1). One mild headache was treated with a single dose of acetaminophen; all other headaches resolved without treatment. Therefore, it is anticipated that the doses selected for this study should be well tolerated and have clinically relevant PD effects in patients with pemphigus.

Further consideration was given to the desired level of FcRn blockade to achieve suppression of IgG to a range that has been previously correlated with disease remission induced by immunoadsorption in autoimmune disorders such as pemphigus vulgaris and myasthenia gravis (ie, >50% decrease in total IgG from baseline) (Blaha et al., 2011; Eming and Hertl, 2006; Kohler et al., 2011).

The Sponsor also considered the potential effects of inhibiting FcRn function as they relate to IC associated innate and adaptive immunity. From the NHP studies, single doses of SYNT001 produced a dose-dependent decrease in total IgG and a further decrease was seen with repeated weekly doses up to a maximum of 70% reduction at 100 mg/kg. This magnitude of total IgG reduction is approaching the expected maximal 90% inhibition of FcRn function based on murine studies performed by the Sponsor and others (Nixon et al., 2015; Roopenian et al., 2003). In the recently completed Phase 1a trial with SYNT001 in healthy volunteers a single dose caused a maximum average 50% drop in total IgG with IV dosing at 30 mg/kg. Based on the

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NHP studies further reductions are expected following multiple dosing. A corresponding decrease in pathogenic autoantibodies is anticipated.

A semi-mechanistic model of FcRn-IgG interactions and FcRn inhibition with SYNT001 was jointly developed by Applied BioMath and the Sponsor. The model was designed to simulate PK and PD responses to various dosing regimens of SYNT001 to inform clinical trial design. Initial simulations were able to capture both PK and PD responses to single doses of SYNT001 from a single-ascending dose study in healthy volunteers and predict multiple dose responses from ongoing studies with good fidelity. The model predicted an IgG reduction of approximately 75% by Day 33, which was determined to be acceptably close to the actual mean IgG reduction of 59% by Day 30 observed in patients. Subsequent iterations of the model have used patient data from ongoing patient studies to further calibrate dose responses. In the most recent simulations, multiple dosing scenarios have been explored, including responses to weekly, bi-weekly, and loading doses. A simulated dosing regimen consisting of three weekly loading doses of 30 mg/kg SYNT001 followed by every other week maintenance doses of 10 mg/kg SYNT001 achieved a nadir IgG reduction of approximately 78% between Days 21 and 28 and maintained an IgG reduction between approximately 50% and 68%. This level of total IgG reduction has been associated with clinical efficacy in early studies of SYNT001-treated pemphigus subjects, and represents a target for future studies in other indications. This regimen of 30 mg/kg loading doses and 10 mg/kg maintenance doses was determined to be the optimal starting regimen to achieve meaningful IgG reduction while maximizing patient safety. Future cohorts may increase the maintenance doses to 20 mg/kg SYNT001, which the model predicts will achieve greater IgG reductions between approximately 55% and 72%. Given the rigorous biological approach taken in the development of the model, simulations of dosing schedules can be considered reliable for the purpose of planning clinical trials.

Several recently completed non-clinical studies support the proposed Cohort 2 dose and dosing regimen. A recently completed 27-week dose-response good laboratory practice (GLP) toxicology study in non-human primates assessed the long-term safety, toxicology, and toxicokinetics of weekly doses of SYNT001. Twenty-seven (27) once weekly 10-minute infusions of SYNT001, at doses of 5, 30, or 100 mg/kg, to cynomolgus monkeys was associated with non-adverse test article-related clinical effects and clinical pathology observations at ≥5 mg/kg. SYNT001 produced dose-dependent reduction of serum IgG levels without affecting IgA, IgM or albumin levels. The NOAEL of SYNT001 was 100 mg/kg following 17 infusions and 30 mg/kg following 27 infusions.

As indicated above, in the recently completed Phase 1a healthy male volunteer study, single doses of SYNT001 up to and including 30 mg/kg have been well tolerated. There were no dose limiting toxicities (DLTs), serious adverse events (SAEs), or any other safety concerns identified. No adverse events (AEs) were observed in the 1 and 3 mg/kg dose cohorts. The only moderate (Grade 2) AE observed was a single instance of headache in the 10 mg/kg cohort. Other subjects had mild (Grade 1) AEs at 10 mg/kg. In Cohort 4 (30 mg/kg), five subjects received SYNT001. All five subjects experienced AEs; all were mild (Grade 1), transient and resolved spontaneously without intervention. The most commonly reported AEs were headache.

A preliminary assessment of safety was conducted by SYNT001 Pemphigus Study SYNT001-103 Dose Escalation Committee (DEC). Seven subjects with pemphigus were treated with

10 mg/kg IV weekly doses over a period of 5 weeks. Overall, SYNT001 10 mg/kg IV was well tolerated. Headache (Grade 1 or 2, self-limited) was the only drug-related AE that was reported in more than one subject. Total IgG and CIC biomarkers were reduced by 59% and 50% respectively, from baseline levels following the fifth dose, returning to baseline within 1 to 2 months. Additionally, preliminary evidence of clinical efficacy as measured by a clinically validated scoring metric, the Pemphigus Disease Area Index, was observed across the population. The DEC approved a dose escalation of SYNT001 from 10 mg/kg IV weekly doses for 5 weeks to 30 mg/kg IV weekly doses for 5 weeks.

Given these preliminary data in non-clinical toxicology species and human subjects, as well as supporting evidence from the computational model, it is anticipated that the doses and dose regimens selected for this study will be well tolerated and will demonstrate clinically relevant pharmacodynamic effects and efficacy in patients with pemphigus. For a summary of findings from the single dose clinical study in healthy subjects and further details regarding the nonclinical findings, please refer to the SYNT001 Investigators Brochure.

2.3 Compliance Statement

This study will be conducted in compliance with Good Clinical Practice (GCP), including the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines and Food and Drug Administration (FDA) regulations, consistent with the principles outlined in the Declaration of Helsinki. In addition, the Investigator agrees to adhere to all applicable local laws and regulatory requirements relevant to the use of new therapeutic agents.

The study will be conducted in compliance with the protocol. The appropriate Institutional Review Boards (IRBs) must approve the protocol, any amendments, and the subject informed consent form (ICF) prior to implementation.

Freely given written informed consent must be obtained from every subject prior to participation in this clinical trial. As part of this procedure, the Investigator must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the study subject is aware of the potential risks, inconveniences, or AEs that may occur. The study subject should be informed that he/she is free to withdraw from the study at any time. He/she will receive all information that is required by federal regulations and ICH guidelines. The Investigator or designee will provide the Sponsor with a copy of the IRB-approved informed consent form prior to the start of the study. The rights, safety, and well-being of participating subjects are the most important considerations and should prevail over interests of science and society.

Study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). This trial will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

3. STUDY OBJECTIVES AND ENDPOINTS

Primary Objectives	Primary Endpoints		
Safety: To evaluate the safety of IV infusions of SYNT001 at different dose levels and dosing regimens in subjects with pemphigus (vulgaris or foliaceus)	Safety: The evaluation of SYNT001 safety based on vital signs, physical examinations, electrocardiograms (ECGs), clinical safety laboratory tests, the incidence of adverse events (AEs), treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) summarized by dose and dosing regimen, severity, and relationship to study drug		
Dose Selection: To determine a MED of SYNT001 as assessed by (i) total IgG level nadir and (ii) the proportion of subjects that meet the criteria for response by Pemphigus Disease Area Index total activity score (PDAI)	Dose Selection: The determination of dose and dosing regimen of SYNT001 that achieves (i) total IgG level nadir decrease by ≥60% and ≤90% from baseline and (ii) a PDAI total activity score of ≥50% reduction from baseline to allow further clinical development in subjects with pemphigus (vulgaris or foliaceus)		
Secondary Objectives	Secondary Endpoints		
To evaluate the efficacy of doses of SYNT001 at different dose levels and dosing regimens on pharmacodynamics (PD) biomarkers	The evaluation of PD biomarkers based on absolute serum levels and percent change from baseline of total IgG, IgG subtypes (IgG1-4), immunoglobulin A (IgA), immunoglobulin M (IgM), albumin, and CIC summarized by dose, dosing regimen and visit		
To determine the pharmacokinetics (PK) of SYNT001 following IV infusions at different dose levels and dosing regimens	The determination of PK parameters including half-life ($t_{1/2}$), maximum serum concentration determined directly from the concentration-time profile (C_{max}), observed time of peak serum concentration (T_{max}), area under the serum concentration-time curve from pre-dose (time ₀) to 24 hours post-dose (AUC ₀₋₂₄), and area under the serum concentration-time curve from pre-dose (time ₀) to infinity (AUC _{0-∞}), (Cohort 1); maximum serum concentration determined directly from the maximum serum concentration and corresponding T_{max} (Cohort 2 onwards) summarized by dose, dosing regimen, visit and time point		
To assess the efficacy of doses of SYNT001 at different dose levels and dosing regimens on disease markers	 The assessment of pemphigus disease activity by responses on the PDAI based on absolute and percent change from baseline, summarized by dose, dosing regimen and visit The assessment of pemphigus disease activity by pathogenic antibody levels based on absolute and percent change from baseline of serum anti-desmoglein 1 and 3 antibody (anti-Dsg 1 and anti-Dsg 		

	levels summarized by dose, dosing regimen and visit
To measure the immunogenicity of SYNT001 administered at different dose levels and dosing regimens	The immunogenicity of SYNT001 as determined by presence of anti-SYNT001 binding antibodies and neutralizing antibodies summarized by dose, dosing regimen, visit and time point
Exploratory Objectives	Exploratory Endpoints
To explore the effect of SYNT001 at different dose levels and dosing regimens on biomarkers to understand the pathophysiology of the disease and the SYNT001 mechanisms of action	The exploration of SYNT001 mechanisms of action and effects of SYNT001 on pathophysiology summarized by dose, dosing regimen and visit as determined by:
	 Complement component 3 levels by nephelometry Anti-epithelial cell antibody (AECA) titers by indirect immunofluorescence Fc gamma R2A receptor (FCGR2A) single nucleotide polymorphisms (SNP) by genotyping Presence of disease and inflammatory markers by total RNA sequencing Immunophenotyping including measurements of T cells, monocytes, natural killer (NK) cells and B cells by flow cytometry Urine IgG levels to explore SYNT001 distribution and elimination (Cohort 1 only) Exploratory biomarkers to investigate immune response associated with pemphigus
To determine the impact of different SYNT001 dose levels and dosing regimens on the subject's use of corticosteroids to treat their pemphigus (vulgaris or foliaceus)	The evaluation of corticosteroid use during the study will be summarized by dose, dosing regimen and visit
To assess the impact of SYNT001 on the subject's health-related quality of life (HR-QoL) at different dose levels and dosing regimens	The assessment of SYNT001 impact on subject's health-related quality of life (HR-QoL) by responses to the Autoimmune Bullous Diseases Quality of Life (ABQoL) questionnaire and Skindex-29 scores summarized by dose, dosing regimen and visit
To assess the effect of SYNT001 on the appearance of skin and mucosal lesions at different dose levels and dosing regimens	The qualitative assessment of changes in appearance of skin and mucosal lesions as determined by photography presented by dose, dosing regimen and visit
To quantify the amount of SYNT001 in skin (skin biopsies optional)	The determination of SYNT001 levels in skin biopsies across timepoints (skin biopsies optional) (Cohort 1 only)

4. STUDY DRUG

4.1 Description of SYNT001

SYNT001 is provided in vials containing 5 mL SYNT001 (extractable volume) at a nominal concentration of 50 mg/mL. The product is supplied as a liquid at pH 6.5 ± 0.5 . SYNT001 is diluted in dextrose 5% in water (D5W) to prepare the solution for infusion. SYNT001 will be infused via IV in 250 mL over 1 hour \pm 15 minutes using a 0.2-micron, inline filter.

Investigators may adjust the duration of the infusion if needed to improve tolerability. Infusion of SYNT001 should be completed within 4 hours of preparation as described in the Pharmacy Manual. For detailed information regarding SYNT001 preparation and administration, refer to the Pharmacy Manual.

4.2 Dose Requirements

The specification for host cell deoxyribonucleic acid (DNA) in SYNT001 is <2 pg/mg, the limit of quantitation of the assay. To comply with regulatory guidelines, which specify a maximum level of 10 ng host cell DNA per dose, dosing per subject is limited to 5000 mg SYNT001.

For example, a subject with a body weight of 166 kg and enrolled in the ≤30 mg/kg dose cohort will receive ≤4960 mg SYNT001 per dose. If a subject's body weight extrapolates to an expected dose ≥5000 mg SYNT001, the dose will be capped at 5000 mg to ensure the 5000 mg SYNT001 per dose limit is not exceeded.

4.3 Handling and Storage of SYNT001

All supplies of SYNT001 will be provided by the Sponsor and must be stored refrigerated (2°C to 8°C/36°F to 46°F) in the carton and protected from light, in a securely locked area, accessible to authorized persons only, until needed for dose preparation.

4.4 Study Drug Accountability

The Investigator (or designee) is responsible for maintaining accurate accountability records of the study drug throughout the clinical study. Qualified site personnel will inventory the study drug received and will maintain records of disposition of the drug, including dates, quantity and use. All study drug received at the site must be accounted for on an accountability log provided by the Sponsor. All dispensing and accountability records will be available for Sponsor review. Study drug accountability will be verified during on-site monitoring visits.

Upon the completion or termination of the study, and upon written authorization from the Sponsor, or its representative, all unused and/or partially used study drug should be returned or destroyed at the investigational site, as specified by Sponsor. It is the Investigator's responsibility to ensure that the Sponsor, or its representative, has provided written authorization that procedures for proper disposal of the study drug have been established, and that appropriate records of the disposal are documented and maintained. No unused study drug may be disposed of until fully accounted for by the Sponsor monitor (or designee).

5. STUDY DESIGN

5.1 Study Sites

This study will be conducted at approximately 20 global study sites.

5.2 Overview of Study Design

This is a multicenter, open-label safety study to determine the dose regimen of SYNT001 administered IV in subjects with pemphigus (vulgaris or foliaceus). Up to 8 subjects with a diagnosis of pemphigus (vularis or foliaceus) will receive SYNT001 10 mg/kg weekly x 5 doses (Cohort 1).

Up to 12 subjects with a diagnosis of pemphigus (vulgaris or foliaceus) will receive SYNT001 30 mg/kg weekly x 3 doses (Loading), followed by SYNT001 10 mg/kg every other week x 5 doses (Maintenance) (Cohort 2) (Figure 1). Subjects in each cohort will complete the following periods of assessment: Screening, Treatment, and Follow-Up.

For Cohort 1 details of the dosing schedule and assessments, see Table 2. For Cohort 2 details, see Table 3.

The Dose Escalation Committee (DEC) will consist of the Medical Monitor, an Independent Clinical Expert and the Sponsor Medical Lead. The DEC may request that Investigators, other experts, or members within their organization participate in the review. Additional information on the DEC's responsibilities is provided in Section 9.5 and the DEC Charter.

An overview of the study cohorts is provided in Table 4 and Figure 1 shows a schematic of the study design.

Cohort No.	No. of Subjects	SYNT001 Dose	No. of Doses	Frequency of Doses
1 ^a	Up to 8	10 mg/kg	5	Weekly
2 ^b	Up to 12	Loading: 30 mg/kg ^c	3°	Weekly ^c
		Maintenance: 10 mg/kg ^c	5°	Every other week ^{c, d}

Table 4. Cohort Overview

- a. No more than 3 subjects with pemphigus foliaceus may be enrolled
- b. Two or fewer subjects with pemphigus foliaceus may be enrolled
- c. The dose, number of doses, and frequency of doses in Cohort 2 will be confirmed based on review of safety and PD evaluations, including but not limited to, dose-limiting toxicities, AEs, TEAEs, SAEs, and total IgG levels. Following Sponsor review of emerging safety, PD and efficacy data, the Loading dose may be reduced to 20 or 10 mg/kg weekly and/or the Maintenance dose may be increased to 20 or 30 mg/kg every other week and/or dose frequency may be increased to weekly.
- d. Ongoing safety and PD evaluations may result in modification of the dose and dosing regimen in Cohort 2. See APPENDIX 5 for the corresponding visit schedule.

Subjects will be enrolled at staggered intervals to facilitate adequate safety evaluation before dosing of subsequent subjects

At 24-hour and 7-day intervals described below, all available safety data (including but not limited to dose-limiting toxicities [DLTs], AEs, TEAEs, SAEs, and PD (including but not limited to IgG levels), will be reviewed.

Safety Review of 24-hour Data

The first 2 subjects in each cohort will be dosed at least 24 hours apart. A DEC review of the 24-hour safety data for the first subject in Cohort 1 will be performed to ensure that there are no overt safety concerns before dosing the second subject. The Sponsor Medical Lead and Medical Monitor will conduct the 24-hour safety data review for the first subject in Cohort 2.

Safety Review of 7-day Data

The 7-day safety data for the first 2 subjects in Cohort 1 will be reviewed by the DEC prior to dosing the remaining subjects in the cohort. The Sponsor Medical Lead and Medical Monitor will conduct the 7-day safety data review in Cohort 2.

The 24-hour and 7-day reviews will consider seriousness and severity of AEs/TEAEs/SAEs and relatedness to study drug, vital sign assessments, physical examinations, and clinical laboratory testing.

For further information about dose escalation and study stopping rules, refer to Section 9.5.1 and Section 9.5.2, respectively.

5.3 Randomization and Blinding

This is an open-label study.

5.4 Duration of Subject Participation

The duration of subject participation for each cohort is as follows:

Cohort	Screening	Treatment	Follow-up	Maximum Total	
				Days	Weeks
1	≤14 days	28 days	84 days	126 days	18 weeks
2	≤14 days	84 days	56 days	154 days	22 weeks

6. STUDY POPULATION

6.1 Target Population

This study will be conducted in male and female subjects aged 18 and older with a confirmed diagnosis of pemphigus (vulgaris or foliaceus). Subjects will be enrolled only once in the study and will not be included in subsequent dosing cohorts. Subjects who withdraw for any reason other than an AE may be replaced.

Within Cohort 1, no more than 3 subjects may be enrolled with pemphigus foliaceus. Within Cohort $2, \le 2$ subjects with pemphigus foliaceus may be enrolled.

6.2 Inclusion Criteria

A subject must meet the following criteria to be eligible for the study:

- 1. Willing and able to read, understand, and sign an informed consent form.
- 2. Male or female \geq 18 years of age at the time of screening.
- 3. Documented diagnosis of pemphigus vulgaris or foliaceus based on all 3 of the following criteria:
 - a. Documented clinical history consistent with pemphigus vulgaris or foliaceus (clinical presentation defined as mucosal and/or skin lesions).
 - b. Presence of Anti-Dsg 1 or 3 antibodies above the upper limit of normal (ULN).
 - c. History of at least one positive tissue-based test (eg, biopsy, direct immunofluorescence [DIF]).
- 4. Active disease defined as lesions lasting >2 weeks, and 3 active lesions in skin or mucosa or 2 active lesions with at least one being a skin lesion >1 cm diameter:
 - a. If treated with rituximab or other anti-CD20 mAb, last dose >9 months prior to screening.
 - b. If being treated with other immunosuppressants (ie, azathioprine, mycophenolate mofetil, methotrexate, dapsone, cyclosporine, tacrolimus, sirolimus, or low-dose cyclophosphamide [\leq 100 mg/day]), dose must be stable, defined as \leq 25% change in dose, for 4 weeks prior to screening.
 - c. On stable dose of corticosteroids, defined as ≤ 1 mg/kg of prednisone or equivalent and may not be increased by more than 50% in the 2 weeks prior to screening.
 - d. Allowed topical therapies for pemphigus lesions upon entering the study include petroleum jelly or Aquaphor® for the skin or chlorhexidine for the mouth.
 - e. Stable use of topical low strength hydrocortisone (≤1%), tacrolimus, sirolimus, or pimecrolimus for lesions contributing <10% of the PDAI total activity score for the 4 weeks prior to screening is allowed. Stable use of dexamethasone elixir solution (swish and spit only) for oral lesions for the 4 weeks prior to screening is allowed.
 - f. If not on regular corticosteroids, no pulse corticosteroids are allowed in the 2 weeks prior to screening.
- 5. Body mass index (BMI) $> 18.5 \text{ kg/m}^2$.
- 6. Has a negative pregnancy test documented prior to the first dose of study drug (for women of childbearing potential).

- 7. Females of childbearing potential must agree to be abstinent or else use any two of the following medically acceptable forms of contraception (<1% per year failure rate) from the screening period through the final study visit: oral contraceptive, condom with or without spermicidal jelly, diaphragm or cervical cap with spermicidal jelly, or intrauterine device (IUD). A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception.
- 8. Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months do not require contraception during the study.
- 9. Males with female partners of childbearing potential, including males who are surgically sterile (post vasectomy), must agree to be abstinent or else use a medically acceptable form of contraception from the screening period through the final study visit.
- 10. A PDAI total activity score of >4 at screening.

6.3 Exclusion Criteria

A subject who meets any of the following criteria is ineligible for the study:

- 1. Subject unable or unwilling to comply with the protocol.
- 2. Active non-hematologic malignancy or history of non-hematologic malignancy in the 3 years prior to screening (exclusive of non-melanoma skin cancer and cervical cancer in situ).
- 3. Positive for human immunodeficiency virus (HIV) or hepatitis C antibody.
- 4. Positive for hepatitis B surface antigen.
- 5. Active infection or history of recurrent infections.
- 6. IVIG treatment within 30 days of screening.
- 7. Received any cytotoxic (other than azathioprine) or any non-anti-CD20 mAb therapy in the 3 months prior to screening.
- 8. Any exposure to an investigational drug or device within the 30 days prior to screening.
- 9. Plasmapheresis or immunoadsorption within 30 days of screening.
- 10. Cellular therapy, including chimeric antigen receptor and T-cell (CAR-T), at any time prior to screening.
- 11. Use of any systemic or topical immunosuppressive drugs within 3 months of screening not including dose allowed by the inclusion criteria.
- 12. Serum total IgG <600 mg/dL at screening.
- 13. Subject has any current medical condition that, in the opinion of the Investigator, may compromise their safety or compliance, preclude successful conduct of the study, or interfere with interpretation of the results (eg, a significant pre-existing illness or other major comorbidity that the Investigator considers may confound the interpretation of the study results).
- 14. Any vaccination within 2 weeks of screening.

7. STUDY PROCEDURES

7.1 Informed Consent

All subjects must take part in the informed consent process. Adequate time must be allowed for the subject to ask questions and make a voluntary decision. No protocol-specific procedures, including screening procedures are to be performed until the subject has signed and dated an IRB-approved ICF. Subjects may withdraw consent at any time. Participation in the study may be terminated at any time without the subject's consent as determined by the Investigator.

7.2 Demographics and Medical History

Demographics (age, gender, race and ethnicity) and medical history will be obtained from the subject and recorded on the source document and electronic case report form (eCRF). Medical history will capture the subject's current medical history (current disease processes), past medical status (past disease processes), history of surgery, concomitant treatments, and relevant clinical response to past disease specific treatments including duration and dosing of such treatments.

7.3 Physical Examination

A complete physical examination will include measurements of weight (in kg) and height (in cm; height to be measured only at screening visit) and a review of the following body systems:

- General appearance
- Head, eyes, ears, nose, and throat
- Neck
- Respiratory
- Cardiovascular
- Abdomen
- Neurologic
- Extremities
- Dermatologic
- Lymphatic

Any abnormal and clinically significant findings from the physical examination must be recorded in the appropriate eCRF. Findings at screening and Day 0 (pre-dose) will be recorded as medical history.

7.4 Vital Sign Measurements

Vital sign assessments will include measurements of sitting blood pressure (mm Hg), heart rate (beats per minute), respiration rate (breaths per minute), pulse oximetry, and oral temperature (Celsius). Abnormal results are to be repeated after 5 minutes of rest. See Table 5 for timing window allowances with respect to measurement collection.

When vital signs are to be collected at the same time point as a blood collection, vital signs should be collected first. Vital sign measurements will be collected after the subject has been sitting for 5 minutes. Subjects should be seated quietly for at least 5 minutes in a chair with their backs supported, their feet flat on the floor (legs uncrossed), and their arms bared on a hard surface, with the arm slightly abducted and bent, with palm up and the midpoint of upper arm at heart level. Correct cuff and bladder size should be utilized and the same cuff and arm should be used per subject throughout study.

Vital sign measurements are to be obtained immediately prior to the infusion; 15, 30, and 45 minutes after the start of the infusion; at completion of the infusion; 30 minutes, 1 hour, and 2 hours following completion of the infusion. Abnormalities in vital sign measurements will be graded in severity per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) scale Version 4.03.

Table 5. Timing window allowances for PK/PD sampling, ECG, and vital sign measurements at dosing visits

Time Point	Tolerance Window		
	Cohort 1	Cohort 2	
Pharmacokinetic Sampling			
0 hour	-240 minutes to 0 hour	-240 minutes to 0 hour	
5 minutes post end-of-infusion	±5 minutes	±5 minutes	
1 hour post end-of-infusion	N/A	±15 minutes	
2 hours post end-of-infusion	±15 minutes	±15 minutes	
4 and 6 hours post end-of-infusion	±15 minutes	N/A	
24 hours (1 day) post end-of-infusion	±60 minutes	N/A	
48 hours (2 days) post end-of-infusion	±120 minutes	N/A	
Pharmacodynamic Sampling			
0 hour	-240 minutes to 0 hour	-240 minutes to 0 hour	
24 hours (1 day) post end-of-infusion	±60 minutes	N/A	
48 hours (2 days) post end-of-infusion	±120 minutes	N/A	
ECG			
5 minutes post end-of-infusion	±10 minutes	±10 minutes	
Vital Signs ^a			
0 hour	-240 minutes to 0 hour	-240 minutes to 0 hour	
15, 30, and 45 minutes after start of infusion	±5 minutes	±5 minutes	
At completion of the infusion	±10 minutes	±10 minutes	
30 minutes, 1 and 2 hours post end-of-infusion	±10 minutes	±10 minutes	

7.5 Clinical Laboratory Measurements

Laboratory testing (hematology, urinalysis, serum chemistry, virology, serology, pregnancy tests, PD, PK, and ADAs) will be performed using established methods by a central laboratory. Clinical safety laboratory panels are listed in Table 6. Blood and urine for hematology, serum chemistry, and urinalysis will be prepared using standard procedures. Results will be provided to the Investigator. Aliquots from the PK, biomarker and ADA samples may be retained as back-up for additional testing as necessary. Subjects will be in a seated or supine position during blood collection. Collection times for all safety, PD, and exploratory labs are outlined in Table 2 and Table 3.

Table 6. Clinical Safety Laboratory Panels

Hematology	Serum Chemistry	Urinalysis	
 CBC with differential and blood smear Erythrocyte sedimentation rate 	 Albumin Alkaline phosphatase ALT AST BUN C-Reactive Protein Calcium Carbon dioxide Chloride Creatinine Glucose LDH Phosphorus Potassium Sodium Total and direct bilirubin Total protein Uric acid 	 Appearance Color pH Specific gravity Ketones Protein Glucose Nitrite Urobilinogen Blood/hemoglobin Leukocyte esterase Bilirubin Microscopic examination of sediment: only if the results of the urinalysis dipstick evaluation are positive for blood/hemoglobin 	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; VZV = Varicella-Zoster virus.

Abnormalities in clinical laboratory tests that are considered clinically significant are to be recorded on the AE eCRF page. Laboratory results will be graded using the NCI CTCAE, Version 4.03. If laboratory values constitute part of an event that meets criteria defining it as serious, the event (and associated laboratory values) must be reported as an SAE (see Section 10.2.3).

7.5.1 Pregnancy Testing

Pregnancy testing will be performed for women of childbearing potential. Urine or serum test is acceptable; however, positive urine tests must be confirmed with serum testing.

7.5.2 Virology

Testing for hepatitis C antibody, hepatitis B surface antigen, and HIV antibody will be performed at screening.

7.5.3 Serum Tetanus Antibody and Varicella-Zoster Virus Antibody Testing

Samples for serum tetanus antibody and VZV antibody testing are to be collected. Any subject whose baseline value for tetanus or VZV was above the protective level at baseline, and is not within 30% of the baseline value or is below the protective level by the end-of-study visit, will be referred to their primary care physician for further management.

7.5.4 Pharmacokinetics (PK) Sampling

The following PK parameters will be studied in Cohort 1: $t_{1/2}$, C_{max} , T_{max} , AUC_{0-24} , and $AUC_{0-\infty}$. For Cohort 2, the PK parameters studied will be C_{max} and T_{max} . For Cohort 2, the PK parameters studied will be maximum serum concentration of SYNT001 and the associated T_{max} .

Specific collection times and timing window allowances are detailed in Table 5. Detailed instructions for sample collection and preparation will be provided in a separate laboratory manual.

7.5.5 Pharmacodynamic Sampling

PD samples will be collected for analyses throughout the study. Measurements for albumin will be derived from the clinical safety laboratory results. Specific collection times are detailed in. Samples for each type of PD will be collected according to the schedule shown in Table 7.

Table 7. Pharmacodynamic Assessments

Parameter	Collection Time Points	
	Cohort 1	Cohort 2 ^a
Immunoglobulins: • IgG • IgG subtypes (IgG1-4) • IgA • IgM	Screening and Days 0, 1, 2, 5, 7, 12, 14, 19, 21, 28, 29, 30, 33, 42, 56, 84, and 112	Screening and Days 0, 7, 14, 28, 42, 56, 70, 84, 91, 112, and 140
Circulating immune complexes (CIC)	Days 0, 5, 7, 12, 14, 19, 21, 28, 33, 42, 56, 84, and 112	Days 0, 7, 14, 28, 42, 56, 70, 84, 91, 112, and 140
Albumin	Screening and Days 0, 7, 14, 21, 28, 33, 42, 56, 84, and 112	Screening and Days 0, 7, 14, 28, 42, 56, 70, 84, 91, 112 and 140
Anti-Dsg (1 and 3) antibody titers	Screening and Days 0, 7, 14, 33, 56, 84, and 112	Screening and Days 0, 7, 14, 28, 42, 56, 70, 84, 91, 112, and 140
C3 and AECA levels by indirect immunofluorescence	Days 0, 14, 33, 56, 84, and 112	Screening and Days 0, 7, 14, 28, 42, 56, 70, 84, 91, 112, and 140
Exploratory biomarkers (RNAseq, urine IgG) ^b	Days 0, 14, 33, 56, 84, and 112	Days 0, 28, and 91
Immunophenotyping by flow cytometry for measurement of T cells, monocytes, NK cells, and B cells	Days 0, 28, and 56	Days 0, 28, and 91
Exploratory biomarker (FCGR2A SNP, via buccal swab)	Day 0	Day 0
Exploratory pemphigus immune response biomarkers	Days 0, 5, 7, 12, 14, 19, 21, 28, 33, 42, 56, 84, and 112	Days 0, 7, 14, 28, 42, 56, 70, 84, 91, 112, and 140

^a Ongoing safety and PD evaluations may result in modification of the dosing regimen from every other week to weekly. See APPENDIX 5 for the corresponding visit schedule.

See Table 5 for timing window allowances with respect to measurement collection. More information, including detailed instructions for sample collection (including collection tubes) and preparation will be provided in a separate laboratory manual.

7.5.6 Immunogenicity Testing

SYNT001 is being developed for the acute and chronic therapy of autoimmune disorders. Although SYNT001 is a humanized IgG4 mAb, exposure to SYNT001 in clinical trials could result in the development of ADAs, with potential consequences ranging from neutralization with possible lessening of drug efficacy to safety consequences such as allergic reactions. Testing will first detect binding ADAs. Then, for all confirmed positive samples, an ADA titer will be determined and there will be testing for neutralizing antibodies using a validated cell-based assay.

More information, including detailed instructions for sample collection and preparation will be provided in a separate laboratory manual.

^b Urine IgG collected in Cohort 1 only.

7.6 12-Lead Electrocardiogram (ECG)

On dose administration days, digital 12-lead ECG measurements will be obtained at 5 minutes after the completion of the infusion. When ECGs are to be collected at the same time point as a blood collection, ECGs should be collected first. All ECGs are to be performed with the subject in a supine position having rested in this position for at least 5 minutes before each reading. ECGs are to be performed in triplicate, each at an interval of 1 to 2 minutes apart (Cohort 1) or approximately 1 minute apart (Cohort 2). See Table 5 for timing window allowances with respect to performing ECG.

The following ECG parameters will be collected: PR interval, RR interval, QRS interval, and QT interval. The ECG findings will be evaluated by a qualified physician for the presence of abnormalities (qualitative assessment). The physician will assess each ECG as normal, abnormal/not clinically significant, or abnormal/clinically significant.

Normal corrected QT interval using Fridericia's formula (QTcF) is ≤450 msec.

Abnormalities in the ECG that appear following therapy or that result in clinical signs and symptoms are considered clinically significant for the purposes of this study and will be recorded on the AE eCRF.

7.7 Pemphigus Disease Area Index (PDAI)

Pemphigus severity and disease activity will be measured using the PDAI in regions where a validated questionnaire is available. A PDAI total activity score will be determined at screening. To be eligible for study participation, the patient's grade by disease severity must be >4. Assuming subject eligibility, the PDAI will be administered during Treatment Period and Follow-up Period. Disease severity categories by PDAI are mild (0 to 8), moderate (9 to 24), and severe (\geq 25) (Shimizu et al., 2014). The Investigator will determine a PDAI score as follows: 0 to 250 points for disease activity (\leq 120 for skin, \leq 10 for scalp, and \leq 120 for mucosa), and 0 to 13 points for damage (\leq 12 for skin and \leq 1 for scalp) (Rosenbach et al., 2009). See Appendix 2.

7.8 Study Drug Administration

SYNT001 will be given as a 250-mL IV infusion over 1 hour \pm 15 minutes using a 0.2-micron, inline filter.

7.9 Photographs

Photographs will be taken of active lesions and follow-up photographs will be taken of the same areas at timepoints indicated in Table 2 and Table 3. Subjects who begin a steroid taper will have additional photographs taken at the clinic visit during which the decision to begin the taper is made. A separate manual describing the procedures for taking photographs will be provided.

7.10 Health-Related Quality of Life Assessments

For Cohort 2, health-related quality of life will be assessed using ABQoL and Skindex-29 in regions where a validated questionnaire is available. The ABQoL questionnaire was developed

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in Australia as a patient-based measure to quantify disease burden, monitor disease activity and evaluate response to therapeutic intervention in patients with autoimmune bullous disease (Sebaratnam et al., 2013; Sebaratnam et al., 2015) (Appendix 3). Skindex-29 was developed to measure the effects of skin disease on patients' quality of life using a self-administered 30-question dermatology survey (Chren et al., 1996) (Appendix 4).

7.11 Adverse Event Assessments

Information regarding the occurrence of AEs will be collected from the time the subject signs the informed consent form and continuing through the last study visit. Findings at screening and Day 0 (pre-dose) will be recorded as medical history. Any known untoward event that occurs beyond the AE reporting period that the Investigator assesses as related to study drug also should be reported as an AE. Clinical AEs will be graded using the NCI CTCAE, Version 4.03 (Appendix 1).

Note: AEs resulting in a subject's permanent discontinuation from the study, regardless of seriousness or relationship to study drug, MUST be promptly reported to the Sponsor. Additionally, subjects must be followed until return to normal and/or resolution of the AE.

See Section 10 for more information.

7.12 Prior and Concomitant Medications

All treatments a subject receives within 14 days prior to enrollment through the end of the study will be documented on the source document and eCRF. A history of treatments taken for the primary disease, even if not taken within the 14 days prior to enrollment, will be collected.

Permitted Medications

Concomitant medication and treatment for co-existing conditions, including those for pemphigus, are permitted if not listed as prohibited.

- 1. Topical antibiotics to treat active infections that occur during the study.
- 2. Topical or systemic treatments for oral candidiasis.
- 3. Topical lidocaine for transient pain relief as needed.
- 4. Concomitant treatment that is medically indicated for any AEs the subject experiences during the study.
- 5. Medication for potential infusion-related reactions (IRRs) including post-infusion headache: The Investigator may recommend prophylactic use of acetaminophen, IV hydration, diphenhydramine, histamine₂ (H₂) blockers (eg, ranitidine, famotidine), etc to manage potential IRRs.
- 6. Low-strength corticosteroids (eg, hydrocortisone ≤1%) applied to a single lesion contributing <10% of the PDAI total activity score.
- 7. Topical tacrolimus, sirolimus or pimecrolimus applied to a single lesion contributing <10% of the PDAI total activity score.
- 8. Dexamethasone elixir solution for oral lesions if dose remains stable throughout trial participation (swish and spit only).

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9. Stable regimen of the following systemic immunosuppressants: azathioprine, mycophenolate mofetil, methotrexate, dapsone, cyclosporine, tacrolimus, sirolimus, corticosteroids, or low dose oral cyclophosphamide (≤100 mg/day).

Fourteen days after the final dose of SYNT001, corticosteroids may be tapered at the Investigator's discretion.

Prohibited Medications

Use of the following medications will not be permitted during the study unless specified above as permitted:

- 1. Rituximab or other anti-CD20 antibody
- 2. Monoclonal antibodies other than study drug
- 3. Any topical or systemic immunosuppressive drugs apart from those that are listed as permitted.
- 4. IV corticosteroids prior to infusion (except in subjects who received corticosteroids for treatment of a prior IRR to SYNT001)
- 5. Any investigational drug or device
- 6. Vaccinations within 2 weeks of screening through 28 days following final dose of study drug

Corticosteroids

Before enrollment

The dose of corticosteroids taken for pemphigus or any other condition prior to screening must be at a dose ≤ 1 mg/kg and the dose level must have not increased in dose level by more than 50% in the 2 weeks prior to screening. No pulse dosing of steroids is permitted in the 2 weeks prior to screening.

From screening until 2 weeks after the last dose of SYNT001

The dose of corticosteroids taken for pemphigus or any other condition should remain stable (<10% change in dose level) from screening until 2 weeks after the last dose of SYNT001. Corticosteroids should neither be started nor discontinued during this period with the exception of subjects who experience an IRR that requires corticosteroids as part of the management of the IRR. Such subjects may receive corticosteroids prophylactically prior to subsequent SYNT001 infusions at the discretion of the Investigator.

From 2 weeks after the last dose of SYNT001 until end of study participation

At the discretion of the Investigator, but only after at least 2 weeks beyond the last dose of SYNT001, a slow corticosteroid taper may be started as per the following suggested schedule:

• If on >30 mg of prednisone per day, decrease by no more than 10 mg every two weeks until a final dose.

If per the Investigator's judgement, the subject would benefit from a change to the pemphigus treatment beyond the allowed steroid taper, this will be considered on a case-by-case basis in consultation with the Sponsor.

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7.13 Skin Biopsy

In Cohort 1, optional skin biopsy samples from lesional or non-lesional skin will be collected to analyze SYNT001 levels.

8. STUDY ASSESSMENTS

Study assessments are performed on a weekly basis and will be comprised of the following periods: Screening, Treatment (including Baseline [Day 0]), and Follow-Up (including End-Of Study). For those subjects that complete all periods in Cohort 1, maximum study duration is 126 days. For those subjects that complete all periods in Cohort 2, maximum study duration is 154 days.

Further detail on specific study assessments is provided in Section 7.

8.1 All Cohorts: Screening Period and First Treatment (Day 0)

8.1.1 All Cohorts: Screening Period (Day -14 to Day -1)

For all cohorts, informed consent must be obtained before any study-specific samples are taken or study-specific tests or evaluations are conducted. The following assessments at the screening visit are to occur within 14 days before dosing. Study eligibility will be based on satisfying all the study inclusion and exclusion criteria (see Section 6).

At the screening visit, information will be collected and subjects will have clinical evaluations as follows:

- Informed consent
- Medical history and demographic data
- Review inclusion and exclusion criteria
- Complete physical examination, including height and weight
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis)
- PDAI (Cohort 2 only)
- Pregnancy test
- Hepatitis and HIV screen
- 12-lead ECG (to be obtained in triplicate after 5 minutes of rest in the supine position)
- Immunogenicity sample collection (*Cohort 2 only*)
- PD sample collection
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - Anti-Dsg1 and Dsg3 antibody titers
 - C3 (*Cohort 2 only*)
 - AECA (Cohort 2 only)
- Concomitant medication assessment
- AE assessment

8.1.2 All Cohorts: Enrollment and First Treatment (Day 0)

For all cohorts, study Day 0 is defined as the date the subject is administered their first dose of study drug. On Day 0, subjects will be asked to come to the clinic and the following procedures will be performed prior to the first dose of study drug:

- Complete physical exam
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry; to be measured immediately prior to the infusion
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis)
- Pregnancy test
- 12-lead ECG (to be obtained in triplicate after 5 minutes of rest in the supine position) (Cohort 2 only)
- Serum tetanus antibody and VZV antibody
- PDAI
- PK baseline sample collection (collected just prior to the start of the study drug infusion)
- Immunogenicity sample collection (collected just prior to the start of study drug infusion)
- PD sample collection (collected just prior to the start of the study drug infusion)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titers
 - C3
 - AECA
 - FCGR2A SNP via buccal swab
 - RNAseq
 - Urine IgG (Cohort 1 only)
 - Immunophenotyping
 - Exploratory pemphigus immune response biomarkers
- Skin biopsy (optional) (Cohort 1 only)
- Photography
- HR-QoL assessments (ABQoL, Skindex-29) (Cohort 2 only)

After the preceding procedures and assessments are completed:

- Study drug administration (record date and time of dose of study drug)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry will be performed at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion

After administration of study drug, the following post treatment procedures and assessments will be performed:

• Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry: 30 minutes, 1 hour, and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest

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- PK sample collection at 5 minutes. Thereafter at 2, 4, 6 hours (Cohort 1) or 1 and 2 hours (Cohort 2) after the completion of study drug infusion; record collection date and time for each PK sample
- 12-lead ECG (to be obtained in triplicate approximately 5 minutes after the completion of study drug infusion

Throughout the study visit, the following assessments will be performed:

- Concomitant medication assessment
- AE assessment

8.2 Cohort 1: Day 1 to 84

8.2.1 Cohort 1: Follow-up Day 1

On Day 1 (24 hours \pm 1 hour from end-of-infusion time on Day 0), the subject will return to the clinic and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature): abnormal results to be repeated after 5 minutes of rest
- PK sample collection (record collection date and time)
- PD sample collection
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
- Skin biopsy (optional)
- Concomitant medication assessment
- AE assessment

8.2.2 Cohort 1: Follow-up Day 2

On Day 2 (48 hours \pm 2 hours from end-of-infusion time on Day 0), the subject will return to the clinic and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature): abnormal results to be repeated after 5 minutes of rest
- PK sample collection (record collection date and time)
- PD sample collection
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
- Skin biopsy (optional)
- Concomitant medication assessment
- AE assessment

8.2.3 Cohort 1: Follow-up Day 5

On Day 5 (120 hours \pm 4 hours from end-of-infusion time on Day 0), subjects may return to the clinic or be visited by an at-home nurse, and the following procedures are to be performed:

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- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature): abnormal results to be repeated after 5 minutes of rest
- PK sample collection (record collection date and time
- PD sample collection
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Exploratory pemphigus immune response biomarkers
- Concomitant medication assessment
- AE assessment

8.2.4 Cohort 1: Treatment Day 7 (Dose 2)

On Day 7 (\pm 6 hours) subjects will return to the clinic and the following procedures are to be performed prior to study drug infusion:

- Complete physical exam
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry; to be measured immediately prior to the infusion
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis)
- PDAI
- PD sample collection (collected just prior to the start of the study drug infusion)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titers
 - Exploratory pemphigus immune response biomarkers

After the preceding procedures and assessments are completed:

- Study drug administration (record date and time of dose of study drug)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry will be performed at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion

After administration of study drug, the following post treatment procedures and assessments will be performed:

• Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry: 30 minutes, 1 hour, and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest

Throughout the study visit, the following assessments will be performed:

- Concomitant medication assessment
- AE assessment

8.2.5 Cohort 1: Follow-up Day 12

On Day 12 (\pm 6 hours), subjects may return to the clinic or be visited by an at-home nurse, and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature): abnormal results to be repeated after 5 minutes of rest
- PD sample collection
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Exploratory pemphigus immune response biomarkers
- If visit performed at the study site: 12-lead ECG to be obtained in triplicate
- Concomitant medication assessment
- AE assessment

8.2.6 Cohort 1: Treatment Day 14 (Dose 3)

On Day 14 (\pm 6 hours) subjects will return to the clinic and the following procedures are to be performed prior to study drug infusion:

- Complete physical exam
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry; to be measured immediately prior to the infusion
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis)
- PDAI
- Immunogenicity sample collection (collected just prior to the start of study drug infusion)
- PD sample collection (collected just prior to the start of the study drug infusion)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titers
 - C3
 - AECA
 - RNAseq
 - Urine IgG
 - Exploratory pemphigus immune response biomarkers
- Skin biopsy (optional)

After the preceding procedures and assessments are completed:

- Study drug administration (record date and time of dose of study drug)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry will be performed at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion

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After administration of study drug, the following post treatment procedures and assessments will be performed:

• Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry: 30 minutes, 1 hour, and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest

Throughout the study visit, the following assessments will be performed:

- Concomitant medication assessment
- AE assessment

8.2.7 Cohort 1: Follow-up Day 19

On Day 19 (\pm 6 hours), subjects may return to the clinic or be visited by an at-home nurse, and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature): abnormal results to be repeated after 5 minutes of rest
- PD sample collection
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Exploratory pemphigus immune response biomarkers
- Concomitant medication assessment
- AE assessment

8.2.8 Cohort 1: Treatment Day 21 (Dose 4)

On Day 21 (\pm 6 hours) subjects will return to the clinic and the following procedures are to be performed prior to study drug infusion:

- Complete physical exam
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry; to be measured immediately prior to the infusion
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis)
- PDAI
- Immunogenicity sample collection (collected just prior to the start of study drug infusion)
- PD sample collection (collected just prior to the start of the study drug infusion)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Exploratory pemphigus immune response biomarkers

After the preceding procedures and assessments are completed:

• Study drug administration (record date and time of dose of study drug)

• Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry will be performed at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion

After administration of study drug, the following post treatment procedures and assessments will be performed:

• Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry: 30 minutes, 1 hour, and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest

Throughout the study visit, the following assessments will be performed:

- Concomitant medication assessment
- AE assessment

8.2.9 Cohort 1: Treatment Day 28 (Dose 5)

On Day 28 (\pm 6 hours) subjects will return to the clinic and the following procedures are to be performed prior to study drug infusion:

- Complete physical exam
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry; to be measured immediately prior to the infusion
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis)
- PDAI
- PK sample collection (collected just prior to the start of the study drug infusion)
- Immunogenicity sample collection (collected just prior to the start of study drug infusion)
- PD sample collection (collected just prior to the start of the study drug infusion)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Immunophenotyping
 - Exploratory pemphigus immune response biomarkers

After the preceding procedures and assessments are completed:

- Study drug administration (record date and time of dose of study drug)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry will be performed at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion

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After administration of study drug, the following post treatment procedures and assessments will be performed:

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry: 30 minutes, 1 hour, and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest
- PK sample collection at 5 minutes and 2, 4, and 6 hours after the completion of study drug infusion; record collection date and time for each PK sample
- 12-lead ECG (to be obtained in triplicate at 5 minutes after the completion of study drug infusion

Throughout the study visit, the following assessments will be performed:

- Concomitant medication assessment
- AE assessment

8.2.10 Cohort 1: Follow-up Day 29

On Day 29 (24 hours \pm 1 hour from end-of-infusion time on Day 28), the subject will return to the clinic and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature): abnormal results to be repeated after 5 minutes of rest
- PK sample collection (record collection date and time)
- PD sample collection
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
- Concomitant medication assessment
- AE assessment.

8.2.11 Cohort 1: Follow-up Day 30

On Day 30 (48 hours \pm 2 hours from end-of-infusion time on Day 28), the subject will return to the clinic and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature): abnormal results to be repeated after 5 minutes of rest
- PK sample collection (record collection date and time)
- PD sample collection
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
- Concomitant medication assessment
- AE assessment

8.2.12 Cohort 1: Follow-up Day 33

On Day 33 (120 hours \pm 4 hours from end-of-infusion time on Day 28), subjects will return to the clinic and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature): abnormal results to be repeated after 5 minutes of rest
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis)
- PDAI
- PK sample collection (record collection date and time)
- PD sample collection
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titers
 - C3
 - AECA
 - RNAseq
 - Urine IgG
 - Exploratory pemphigus immune response biomarkers
- Skin biopsy (optional)
- Photography
- Concomitant medication assessment
- AE assessment

8.2.13 Cohort 1: Follow-up Day 42

On Day 42 (\pm 3 days), subjects will return to the clinic and the following procedures are to be performed:

- Complete physical exam
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature): abnormal results to be repeated after 5 minutes of rest
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis)
- PDAI
- PD sample collection (collected just prior to the start of the study drug infusion)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Exploratory pemphigus immune response biomarkers
- Concomitant medication assessment
- AE assessment

8.2.14 Cohort 1: Follow-up Day 56

On Day 56 (\pm 5 days), subjects are to return to the clinic and the following procedures are to be performed:

- Complete physical exam
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature): abnormal results to be repeated after 5 minutes of rest
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis)
- Pregnancy test
- 12-lead ECG (to be obtained in triplicate after 5 minutes of rest in the supine position)
- Serum tetanus antibody and VZV antibody
- PDAI
- Immunogenicity sample collection
- PD sample collection
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titers
 - C3
 - AECA
 - RNAseq
 - Urine IgG
 - Immunophenotyping
 - Exploratory pemphigus immune response biomarkers
- Skin biopsy (optional)
- Photography
- Concomitant medication assessment
- AE assessment

8.2.15 Cohort 1: Follow-up Day 84

On Day 84 (\pm 5 days), subjects are to return to the clinic and the following procedures are to be performed:

- Complete physical exam
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature): abnormal results to be repeated after 5 minutes of rest
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis)
- Serum tetanus antibody and VZV antibody
- PDAI
- Immunogenicity sample collection
- PD sample collection
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titers

- C3
- AECA
- RNAseq
- Urine IgG
- Exploratory pemphigus immune response biomarkers
- Skin biopsy (optional)
- Photography
- Concomitant medication assessment
- AE assessment

Note: Cohort 1 End-of-Study visit is detailed in Section 8.4.

8.3 Cohort 2: Subsequent Treatments to Follow-up

8.3.1 Cohort 2: Treatment Days 7, 14, 42, 56, 70, and 84

For Cohort 2 Days 7, 14 (all \pm 1 day), 42, 56, 70, and 84 (all \pm 3 days), subjects will return to the clinic and the following procedures are to be performed prior to study drug infusion:

- Complete physical exam
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry; to be measured immediately prior to the infusion
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis)
- PDAI
- PK sample collection (collected just prior to the start of the study drug infusion) (*Cohort 2, Days 7, 14, and 84 only*)
- Immunogenicity sample collection (collected just prior to the start of study drug infusion)
- PD sample collection (collected just prior to the start of the study drug infusion)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titers
 - C3
 - $-\Delta FC\Delta$
 - Exploratory pemphigus immune response biomarkers
- Photography

After the preceding procedures and assessments are completed:

- Study drug administration (record date and time of dose of study drug)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry will be performed at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion

After administration of study drug, the following post treatment procedures and assessments will be performed:

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry: 30 minutes, 1 hour, and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest
- 12-lead ECG (to be obtained in triplicate approximately 5 minutes after the completion of study drug infusion (*Cohort 2, Day 14 only*)
- PK sample collection at 5 minutes and 1 and 2 hours after the completion of study drug infusion; record collection date and time for each PK sample (Cohort 2, Days 7, 14, and 84 only)

Throughout the study visit, the following assessments will be performed:

- Concomitant medication assessment
- AE assessment

8.3.2 Cohort 2: Treatment Day 28

For Cohort 2 Day 28 (\pm 3 days), subjects will return to the clinic and the following procedures are to be performed prior to study drug infusion:

- Complete physical exam
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry; to be measured immediately prior to the infusion
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis)
- Pregnancy test
- 12-lead ECG (to be obtained in triplicate after 5 minutes of rest in the supine position)
- Serum tetanus antibody and VZV antibody
- PDAI
- PK sample collection (collected just prior to the start of the study drug infusion)
- Immunogenicity sample collection (collected just prior to the start of study drug infusion)
- PD sample collection (collected just prior to the start of the study drug infusion)
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titers
 - C3
 - AECA
 - RNAseq
 - Immunophenotyping
 - Exploratory pemphigus immune response biomarkers
- Photography
- HR-Qol (ABQoL, Skindex-29)

After the preceding procedures and assessments are completed:

- Study drug administration (record date and time of dose of study drug)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry will be performed at 15, 30, and 45 minutes after the start of the infusion and at completion of the infusion

After administration of study drug, the following post treatment procedures and assessments will be performed:

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature) and pulse oximetry: 30 minutes, 1 hour, and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest
- PK sample collection at 5 minutes and 1 and 2 hours after the completion of study drug infusion; record collection date and time for each PK sample
- 12-lead ECG (to be obtained in triplicate approximately 5 minutes after the completion of study drug infusion

Throughout the study visit, the following assessments will be performed:

- Concomitant medication assessment
- AE assessment

8.3.3 Cohort 2: Follow-up Day 112

For Cohort 2 Day 112 (\pm 5 days), subjects are to return to the clinic and the following procedures are to be performed:

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature): abnormal results to be repeated after 5 minutes of rest
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis)
- PDAI
- Immunogenicity sample collection
- PD sample collection
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titers
 - C3
 - AECA
 - Exploratory pemphigus immune response biomarkers
- Photography
- Concomitant medication assessment
- AE assessment

8.4 All Cohorts: End of Study or Early Termination Visit; Cohort 1, Day 112; Cohort 2, Days 91 and 140

For Cohort 1 Day 112 (\pm 5 days) and Cohort 2 Days 91 and 140 (\pm 5 days), subjects are to return to the clinic and the following procedures are to be performed:

- Complete physical exam
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature): abnormal results to be repeated after 5 minutes of rest
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis)
- Pregnancy test
- 12-lead ECG (to be obtained in triplicate after 5 minutes of rest in the supine position) (Cohort 2, Days 91 and 140 only)
- Serum tetanus antibody and VZV antibody
- PDAI
- Immunogenicity sample collection
- PD sample collection
 - IgG, IgG subtypes (IgG1-4), IgA, IgM
 - CIC
 - Anti-Dsg (1 and 3) antibody titers
 - C3
 - AECA
 - RNAseq (Cohort 1 Day 112; Cohort 2, Day 91 only)
 - Urine IgG (Cohort 1 only)
 - Immunophenotyping (Cohort 2, Day 91 only)
 - Exploratory pemphigus immune response biomarkers
- Photography
- HR-Qol (ABQoL, Skindex-29) (Cohort 2 only)
- Concomitant medication assessment
- AE assessment

Note: a subject may choose to terminate participation in the study at any time. Under this circumstance, the subject will be encouraged to return as soon as possible for an early termination visit and to receive assessments otherwise scheduled on Day 112 (Cohort 1) or Day 91 (Cohort 2).

9. STUDY RULES

9.1 Subject Withdrawal

Every reasonable effort will be made to keep the subject in the study; however, if a subject withdraws from the study, the Investigator should complete and report the reasons for withdrawal as thoroughly as possible. The reason(s) for termination must be clearly documented on the appropriate page of the eCRF.

Subjects who have received at least one SYNT001 dose and withdraw or prematurely discontinue study drug should be encouraged to attend, at a minimum, the early termination (ET) visit Day 112 (Cohort 1) or Day 91 (Cohort 2). Subjects in Cohort 2 will also be encouraged to attend the remaining follow up visits on Days 112 and 140.

If the subject fails to return for these assessments for unknown reasons, every effort (eg, telephone, email, and letter) should be made to contact them.

The reason(s) for a subject's participation in the study may be prematurely discontinued will be documented and include:

- 1. The subject wishes to withdraw from the study.
- 2. Request by a regulatory agency or Institutional Review Board).
- 3. The subject experiences a significant or intolerable AE.
- 4. The subject experiences a significant adverse change in vital signs, physical examination findings, or clinical laboratory parameter.
- 5. The subject has a need for a concomitant medication that is not permitted by the study protocol.
- 6. The subject experiences generalized impairment or mental incompetence that would result in the subject being unable to understand his or her participation in the study.
- 7. If, in the Investigator's medical judgment, further participation would be injurious to the health and well-being of the subject, or is not in the best interest of the subject.
- 8. Administrative reasons, such as subject non-compliance or a major protocol violation.

If at the discretion of the Investigator with consultation with the Medical Monitor, a subject requires a significant increase in dose(s) of anti-pemphigus medication(s) for the management of pemphigus, the subject should be encouraged to attend, at a minimum, the ET visit Day 112 (Cohort 1) or Day 91 (Cohort 2). Subjects in Cohort 2 will also be encouraged to attend the remaining follow up visits on Days 112 and 140.

9.2 Subject Replacement

Enrolled subjects withdrawn for a reason other than an AE may be replaced.

9.3 Study Discontinuation

The Sponsor has the right to terminate or to stop the study at any time. Reasons for study discontinuation may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other related studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory
- Drug supply issues
- Excessive subject self-withdrawal
- Significant protocol violations (eg, violation of eligibility criteria, dosing errors, missing data for study endpoint analysis)

9.4 Lost to Follow-up

All reasonable efforts should be made to contact any subject lost to follow-up during the study to complete assessments and retrieve any outstanding data. If the subject is unreachable after three good faith attempts, at a minimum, the Investigator should follow up with a registered letter requesting contact so safety data may be collected, recorded, and reported (if necessary).

9.5 Stopping Rules

9.5.1 Dose-Escalation Stopping Rule (Cohort 1)

Dose recommendations will be made by a DEC and will be based on safety and PD evaluations including but not limited to, DLTs, AEs, SAEs, and total IgG levels.

Dose-limiting toxicity (DLT) will be defined generally as severe (Grade 3) AEs occurring in ≥2 subjects that are determined to be clinically significant and considered related to study drug.

If 2 or more subjects at any time in any cohort have Grade 3 AEs that are determined to be clinically significant and considered to be related to study drug, dosing will be halted within that cohort and dose-escalation to a higher dose will not occur. Upon review of the available information, the DEC may reduce the dose by at least 50% prior to enrolling additional subjects.

9.5.2 Study Stopping Rule

If any subject at any time experiences a life-threatening AE (Grade 4) that is considered to be related to study drug, any further dosing in all enrolled subjects will be suspended until the Sponsor Medical Lead has evaluated the event and determined the next appropriate course of action. At any time during the study, the study may be discontinued if the Sponsor Medical Lead determines that further drug exposure would pose an undue risk to subjects.

9.5.3 Individual Stopping Rule

Dosing for any individual subject will be discontinued (ie, no further study drug will be given to that subject) if the subject experiences any study drug-related SAE or any study drug-related

non-serious AE that, in the judgement of the Investigator (following consultation with the Medical Monitor, if desired) or in the judgement of the Sponsor Medical Lead, suggest that it could be unsafe to administer further study drug to that subject.

Subjects who withdraw from this study due to an AE determined to be related to study drug are to be followed until there is:

- Resolution or stabilization of the AE determined to be related
- The subject is lost to follow-up
- The event is otherwise explained

If there is a persistent AE contributing to discontinuation that is determined to be related to SYNT001, subjects must be followed with appropriate medical management until resolution or stabilization. Refer to Section 10 for more information.

Additionally, a subject will be discontinued from further treatment with study drug, at the discretion of the Investigator with consultation with the Medical Monitor, if they require a significant increase in doses of anti-pemphigus medications for the management of pemphigus.

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10. EVALUATION OF SAFETY

10.1 Safety Parameters

Subjects will be monitored continuously throughout the treatment and follow-up period for AEs (acute, delayed, and/or cumulative), as well as for changes in clinical status. Parameters measure/assess safety include physical examinations, vital sign measurements (including pulse oximetry), clinical (safety) laboratory tests (hematology, serum chemistries, urinalysis), concomitant medication assessments, and ECG. Clinical and laboratory AEs will be graded using the NCI CTCAE; Version 4.03 (see Appendix 1).

10.2 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical trial subject associated with the use of a drug, whether considered drug related or not. An AE can be an unfavorable and unintended sign (eg, an abnormal laboratory value finding), a symptom, or a disease temporally associated with the use of a drug, without judgment as to causality. An AE can arise from use of the drug (eg, use in combination with another drug) and from any route of administration, formulation or dose, including an overdose. An AE also includes, but is not limited to, any clinically significant worsening of a pre-existing condition. Examples include:

- Any sign, symptom, physical finding, or laboratory result that has worsened in nature, severity or frequency compared to baseline
- Reactions from an investigational drug, including those occurring because of an overdose, abuse of the study drug, withdrawal phenomena, sensitivity or toxicity
- Concurrent illness that was not present or worsens in nature, severity, or frequency compared to baseline
- Injury or accident
- Exacerbation of a pre-existing condition

Pregnancy is not considered an AE or SAE; however, any pregnancy complication(s) should be recorded as an AE(s) or SAE(s) (if applicable). Elective abortions without complications should not be regarded as AEs, unless they were therapeutic abortions. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE. If a female subject becomes pregnant during the conduct of the study, the Investigator must notify the Sponsor according to the procedures provided in Section 10.5.4.

Planned hospitalization admissions or surgical procedures for a condition known to exist before the subject signed the informed consent are not an AE and should be recorded as medical history. If the planned hospitalization or procedure is executed as planned and without complication, the record in the subject's medical history is considered complete. However, if the event/condition deteriorates in an unexpected manner during the study or following surgery, it must be reported as an AE according to the procedures provided in Section 10.2.1.

10.2.1 Recording an Adverse Event

For data collection, all untoward events that occur after informed consent through the last study visit are to be recorded on eCRFs by the investigational site. All AEs are to be accurately recorded on the **Adverse Event** page of the subject's eCRF. The severity of each AE will be graded using the NCI CTCAE, Version 4.03 (see Appendix 1). The date of onset as well as the end date of the event should be recorded or the event should be entered as "ongoing". In addition, the method used to treat the AE and the outcome of the AE will be noted. The Investigator will assess the relationship of the event to study drug.

10.2.2 Assessment of Causality

A medically qualified Investigator must assess the relationship of any AE (including SAEs) to the use of the study drug, as related or not related, based on clinical judgment and using all available information. The causal relationship between the study medication and the AE will be assessed using one of the following categories:

Not Related: Factors consistent with an assessment of Not Related include:

- Temporal relationship is lacking (eg, the event did not occur within a reasonable time frame following administration of the study medication); or
- Other causative factors more likely explain the event (eg, a pre-existing condition, other concomitant treatments).

Related: Factors consistent with an assessment of Related include:

- There is a positive temporal relationship (eg, the event occurred within a reasonable time frame following administration of study medication); or
- The AE is more likely explained by the investigational product than by another cause (ie, the AE shows a pattern consistent with previous knowledge of the investigational product or the class of the investigational product)

10.2.3 Serious Adverse Events

(Notify Medpace Safety within 24 hours; document on eCRF)

The SAE definition and reporting requirements are in accordance with Title 21 Part Code of Federal Regulations (CFR) 312.32 and the Guidance for Industry and Investigators Safety Reporting Requirements for Investigational New Drug (INDs) and Bioavailability /Bioequivalence Studies.

An AE is considered "serious" if, in the view of either the Investigator or sponsor, it results in any of the following outcomes:

• <u>Death:</u> This includes any death that occurs while the subject is "on study" through the last study visit.

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Note: Death is an outcome of an AE and not an AE. The event(s) that caused death (eg, illness, accident) is the SAE. Death due to any other cause(s) must also be reported as an outcome of the reportable SAE.

- <u>Life-threatening adverse drug event:</u> An AE or suspected adverse reaction is considered "life threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- <u>Inpatient hospitalization or prolongation of existing hospitalization:</u> an AE that requires admission to a hospital for medical and/or surgical intervention.
- In the absence of an AE, the Investigator should <u>not</u> report hospitalization or prolongation of hospitalization as an SAE, as detailed in the following examples:
 - An elective or previously scheduled surgery for a pre-existing condition that has not deteriorated unexpectedly after initiation of treatment (eg, a previously scheduled ventral hernia repair)
 - Hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol
 - Hospitalization or prolongation of hospitalization is part of routine procedure followed by study center
 - o Hospitalization for survey visits, annual physicals, or planned observation
 - Hospitalization for observation with release within 24 hours (eg, an emergency room visit for hematuria that results in a diagnosis of cystitis and discharge to home on oral antibiotics
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect
- <u>Important medical event:</u> An event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.2.3.1 Recording a Serious Adverse Event

When the diagnosis of an SAE is known or suspected, the Investigator should record the diagnosis or syndrome as the primary SAE term, rather than as signs or symptoms. Signs and symptoms may then be described in the event description. For example, dyspnea should not be used as an SAE term if the diagnosis, which caused the dyspnea, is known to be malignant pleural effusion.

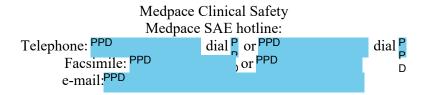
Death should not be recorded as an SAE, but as an outcome of a specific SAE, unless the event preceding the death is unknown. In the exceptional case where the events leading to death are unknown, then death may be used as an event term. If an autopsy was performed, the autopsy the autopsy report should be provided.

10.2.3.2 Reporting a Serious Adverse Event

RESPONSIBILITIES OF THE INVESTIGATOR

Any death, SAE, or pregnancy, experienced by the subject after informed consent through the last study visit, regardless of relationship to study drug, must be promptly reported (within 24 hours of the Investigator becoming aware of the event) by telephone or electronic transmission to the Sponsor (or designee).

Contact information for SAE reporting:



Additionally, the Investigator will be able to contact the **Medical Monitor**:

Medical Safety Contact



The Investigator will report the SAE to his or her IRB in accordance with IRB's standard operating procedures and policies. Adequate documentation must be maintained showing that the IRB was properly notified.

SAEs must be recorded on the SAE form in the electronic data capture (EDC) system. This requirement includes all SAEs that occur after informed consent through the last study visit. The minimum information required for SAE reporting includes identity of investigator, site number, subject number, an event description, SAE term(s), onset date, the reason why the event is serious (ie, the seriousness criteria), and the Investigator's assessment of the relationship of the event to study treatment. Additional SAE information including medications or other therapeutic measures used to treat the event, action taken with the study treatment due to the event, and the outcome/resolution of the event will be recorded. Paper forms for reporting SAEs will be provided to the study sites as back-up in case the EDC system is not accessible.

In all cases, the Investigator should continue to monitor the clinical situation and report all material facts relating to the progression or outcome of the SAE. Furthermore, the Investigator may be required to provide supplementary information as requested by the Sponsor (or designee).

RESPONSIBILITIES OF THE SPONSOR (OR DESIGNEE)

The Sponsor (or designee) will process and evaluate all SAE as soon as the reports are received. For each SAE received, the Sponsor will decide as to whether the criteria for expedited reporting have been met.

The Sponsor (or designee) is responsible for promptly informing the FDA and other regulatory authorities as well as other participating Investigators of the event. Written submission must be made by the Sponsor to the FDA as soon as possible and in no event later than 15 calendar days after the Sponsor's initial notification of the event, or for an event that is fatal or life-threatening no later than 7 calendar days after the Sponsor's initial notification.

EXPEDITED REPORTING

Under FDA ruling (US Code of Federal Regulations, Title 21 CFR Part 312.32) and the ICH Guideline "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A," the Sponsor is required to submit written documentation, in the form of a safety report, detailing:

- Any event associated with the use of the drug, that is both serious and unexpected, or
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.

The Sponsor will submit SAEs that meet the criteria for expedited reporting to the regulatory authorities in accordance with local regulations governing safety reporting.

10.2.4 Follow-Up of Adverse Events and Serious Adverse Events

Any SAE or AE must be followed until either resolution of the event or determination by the Investigator that the event has become stable or irreversible. Appropriate diagnostic tests should be performed and therapeutic measures, if indicated, should be instituted until the event has returned to baseline or until a clinically satisfactory resolution has been achieved. The appropriate follow-up visits must be scheduled and the specific tests repeated or performed as necessary. The status of all AEs will be documented as of the last study visit. If all required information is not available at the time of the initial report, follow-up information will be completed in the EDC system.

10.3 Warnings and Precautions

10.3.1 Vaccinations

Subjects must not receive any vaccinations from within 2 weeks of screening until 28 days following final dose of study drug.

10.3.2 Management of Allergic or Infusion-Related Reactions

As observed with all mAbs administered by IV infusion, infusion-related reactions to SYNT001 are possible. In general, infusion reactions to mAbs observed in human studies typically develop

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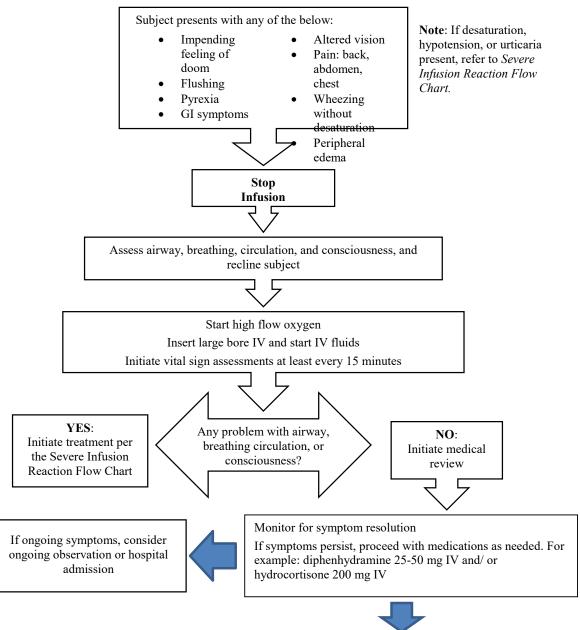
within 30 minutes to 2 hours after the initiation of drug infusion, although symptoms may be delayed for up to 24 hours. These infusion reactions can occur with the first dose of a mAb and are generally mild in severity, although severe and even fatal reactions can occur.

Allergic and/or infusion-related reactions include hypersensitivity reactions and cytokine release syndromes. These reactions are experienced by subjects during or within hours of the infusion of mAb therapy. Symptoms can include flushing, alterations in heart rate and blood pressure, dyspnea, bronchospasm, back pain, fever, urticaria, edema, nausea, and all types of rashes. Anaphylaxis is recognized as a severe, life-threatening, generalized, or systemic reaction. This is a medical emergency characterized by rapidly developing life-threatening airway and/or breathing and/or circulation problems usually associated with skin or mucosal changes.

Management of Grade 1 infusion reactions include interrupting the infusion or decreasing the rate of infusion by 50% and observing. Symptoms may also be treated as needed with medications such as diphenhydramine, hydrocortisone, or acetaminophen, either alone or in combination, depending on the subject's signs and symptoms. If the infusion is interrupted or the infusion rate is decreased, it is important to note that all study drug infusions must be completed within 4 hours of SYNT001 preparation.

Management of Grade 2 and higher infusion reactions should include stopping the infusion of study drug. Continued treatment with SYNT001 is prohibited following Grade 2 or higher infusion reactions. See Figure 2 and Figure 3 for details on the management of Grade 2 and Grade 3 infusion reactions. Allergic or IRRs will be graded in severity and managed based on NCI CTCAE Version 4.03 (see Table 8).

Figure 2. Management of Moderate (Grade 2) Infusion Reactions



If symptoms and signs resolve completely either spontaneously or after administration of diphenhydramine with or without hydrocortisone, consider rechallenge:

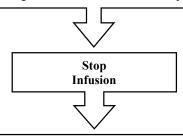
Wait at least 20 minutes following medication administration before commencing rechallenge at an infusion rate of 50% or less of the initial infusion rate or

Consider pre-medicating the subject with the same medication(s) 20-30 minutes in advance of subsequent administrations of SYNT001 and starting infusion at 50% of the planned infusion rate for the first 30 minutes, then returning to the intended infusion rate in the absence of any infusion reaction. If the infusion is interrupted or the infusion rate is decreased, it is important to note that all study drug infusions must be completed within 4 hours of SYNT001 administration.

Figure 3. Management of Severe (Grade 3 or Higher) Infusion Reactions

Subject presents with any of the below:

- Urticaria
- Airway threatened by angioedema
- Angioedema: Lip, mouth, facial swelling
- Respiratory compromise wheezing, dyspnea, stridor or hypoxia (O₂ saturation <90%)
- BP <90 mmHg SBP or >30% decrease from patient baseline



Start basic life support:

- High oxygen flow
- On bed, head down, legs up
- Large bore IV cannula, 1 L normal saline STAT
- Initiate vital signs at least every 15 minutes



Consider (under medial direction):

Epinephrine 1:1000

• 0.3 mg (0.3 mL) IM into lateral thigh



Airway Threatened: Nebulized epinephrine 1:1000, 3–5 mL (3–5 mg)

Bronchospasm: Nebulized salbutamol 5 mg

(Wheeze or Hypoxia) Consider: Intubation / nebulized epinephrine

Hypotension: Place on cardiac monitor

(Systolic BP <100 mmHg) Further epinephrine 1:1000, 0.3 mg IM and

IV normal saline bolus 20 mL/kg STAT as needed

Have vasopressin on hand



Transfer to Emergency Room/ICU Observe until all symptoms resolved.

 Table 8.
 Grading and Management of Allergic or Infusion-Related Reactions

Adverse			Grade		
Event	1	2	3	4	5
Infusion- related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal antiinflammatory drugs [NSAIDS], narcotics, IV fluids): prophylactic medications indicated for ≤24 hours	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement, hospitalization indicated for clinical sequelae	Life- threatening consequences; urgent intervention required	Death
Allergic reaction	Transient flushing or rash, drug fever <38.0°C. Intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids): prophylactic medications indicated for ≤24 hours	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement, hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates)	Life- threatening consequences; urgent intervention required	Death
Anaphylaxis	_	_	Symptomatic bronchospasm, with or without urticarial; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life- threatening consequences; urgent intervention required	Death
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids): prophylactic medications indicated for ≤24 hours	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement, hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates)	Life- threatening consequences; pressor or ventilator support indicated	Death

Abstracted from NCI CTCAE Version 4.03.

10.3.3 Potential Immune Effects

An antibody blocking FcRn is anticipated to have several effects. These include acceleration of catabolism of IgG, but not other immunoglobulin isotypes such as IgA and IgM, leading to dose-dependent decreases in circulating IgG levels by up to an estimated 50% from the baseline levels

after a single dose and further decreases after multiple doses up to a 70% to 80% reduction. Based on studies in humans, it is expected that with a single dose, the nadir of this effect will occur approximately 5 days after dosing. The time course of recovery of IgG following dosing in the Phase 1a study suggests that a return to within 30% of baseline levels observed at pretreatment occurs within 4 weeks after a single dose and within 4 weeks after multiple doses as shown in NHPs.

Given the normal adult range of total IgG of 500 to 1600 mg/dL (Agarwal and Cunningham-Rundles, 2007; Furst, 2009; Gonzalez-Quintela et al., 2008; Jolliff et al., 1982; Keystone et al., 2007; McMillan et al., 1997; van Vollenhoven et al., 2013), with a mean of 1150 mg/dL, a 50% decrease in mean total IgG would translate to 575 mg/dL and a 50% decrease from the low end of the normal range used for the inclusion criteria of 600 mg/dL in this study would be to 300 mg/dL. An 80% decrease from baseline after multiple doses would result in IgG levels of 230 mg/dL and 120 mg/dL, respectively. While these levels are in the range found in patients with primary humoral immunodeficiency (Ameratunga et al., 2013), the levels will be transient. Further, as reported for other therapies used for pemphigus, the temporary (ie, less than 4 months) depletion of IgG (up to 95% reduction of total IgG as seen with immunoadsorption) does not appear to impart an increased risk of infection (Eming and Hertl, 2006; Furst, 2009; Keystone et al., 2007; Schmaldienst et al., 2001; van Vollenhoven et al., 2013). Study subjects will be monitored clinically for any infection. Further, commercial IVIG can be given to immediately restore IgG levels in case of a bacterial infection occurring while their IgG levels are decreased.

An antibody that blocks FcRn is expected to also down-modulate innate and adaptive immunity and the catabolism of IgG-containing ICs. Specifically, it is expected that anti-FcRn will promote the clearance of IgG-containing ICs and the effects of these ICs on stimulating innate immune cell production of inflammatory cytokines (eg, interleukin 12 [IL-12], interferon-γ, and tumor necrosis factor) and inhibit the processing and presentation of antigens contained within ICs and thus the antigen-specific activation of CD4⁺ and CD8⁺ T-cells. Therefore, subjects with pre-existing conditions that are dependent upon IgG antibodies, such as chronic infections (eg, HIV, hepatitis B virus [HBV] or hepatitis C virus [HCV]), will be excluded from this study, as will subjects with active infection, in general.

10.4 Events of Special Interest

Not applicable.

10.5 Other Safety Considerations

10.5.1 Laboratory Data

All laboratory data obtained during the study should be reviewed. Any abnormal value that leads to a change in subject management (eg, requirement for additional medication or monitoring) or is determined to be of clinical significance by the Investigator should be reported as an AE and/or SAE as appropriate, unless this value is consistent with values obtained before entry into the study.

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10.5.2 Medication Errors

Any medication error that results in an AE, even if it does not meet the definition of serious, requires reporting within 24 hours to the safety Medical Monitor. Refer to Section 10.2.3.2 for more information.

10.5.3 Overdose

For the purposes of this study, an overdose of SYNT001 is defined as a dose that is two-fold higher than the intended dose for the subject. As all dosing for this study will be conducted in a controlled clinical setting, an overdose is not anticipated. In the unlikely event an overdose should occur, it should be reported as an AE.

10.5.4 Pregnancy

If a female subject or the female partner of a male subject becomes pregnant during the course of the study, the Investigator must report the pregnancy to Medpace Safety using the **Pregnancy Reporting Form** within **24 hours** of becoming aware of the event. The Investigator must obtain consent to collect pregnancy information (including the status of the newborn, if applicable).

If some of the information required for completion of the Pregnancy Reporting Form is unavailable at the time of the initial report, follow-up reports will be completed and submitted within 24 hours of becoming aware of the new information. Any pregnancy will be followed through delivery for the observation of any SAEs. Any SAE that occurs during pregnancy must be recorded on the SAE report form in the EDC system (eg, maternal serious complications, therapeutic or spontaneous abortion, ectopic pregnancy, stillbirth, neonatal death, congenital abnormality, birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs (see Section 10.2.3.2).

11. STATISTICAL CONSIDERATIONS

11.1 General Design

This study is being conducted to evaluate the safety, tolerability, PK, PD, activity, and immunogenicity of SYNT001 in pemphigus patients.

11.2 Study Populations

Three populations will be employed in the analysis of study data:

- The Safety population will consist of all subjects who have received at least one dose of study drug.
- The **PD** population will consist of all subjects who receive at least one dose of study drug and have post-dose PD data available.
- The **PK** population will consist of all subjects who receive at least one dose of study drug and have post-dose PK data available.

Primary safety analyses will be performed on the Safety population. Demographics, subject disposition, screening, and baseline characteristics will be summarized for the Safety, PK, and PD populations, where appropriate.

11.3 Sample Size Justification

Formal sample size calculations were not performed. The number of subjects was chosen based on feasibility and was considered sufficient to meet the study objectives.

11.4 Statistical Analysis

11.4.1 Statistical Analysis Plan

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP). The SAP may modify the plans outlined in the protocol; however, any deviations from the previously approved statistical plan will be described and justified in a SAP amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate and will be described in the SAP. The SAP will be finalized prior to database lock.

Statistical analyses will be performed using Statistical Analysis System (SAS) software version 9.4 or later (Cary, NC). All clinical data captured will be provided in data listings.

Methods of handling of missing data for different endpoints will be further specified in the SAP. In general, where individual data points are missing because of insufficient samples, dropouts, or other reasons, the data will be analyzed based on reduced denominators unless specified otherwise in the SAP.

11.4.2 Statistical Methodology

All clinical data captured will be provided in data listings. Subject disposition, demographic information, and baseline characteristics will be presented. Baseline will be defined at the last value obtained prior to the first dose of study drug. Results will be summarized by dose level and cohort. Any discrepancy between treatment to be given and treatment received will be accounted for in these displays.

Continuous data will be summarized using descriptive statistics: number of subjects (N), number of observations (n), mean, median, standard deviation (SD), minimum, and maximum.

Categorical data will be summarized using frequencies and percentages. When categorical data will be presented, the percent will be suppressed when the count is zero to draw attention to the non-zero counts. The denominator for all percentages, unless otherwise specified, will be the number of subjects in the specified analysis population.

11.4.3 Analysis of Primary Endpoints

11.4.3.1 Safety Analysis

All statistical analysis of safety outcomes will be descriptive. The evaluation of SYNT001 based on vital signs, physical examination, ECGs, clinical safety laboratory tests, the incidence of AEs, TEAEs, and SAEs will be summarized by dose and dose regimen, severity, and relationship to study drug.

TEAEs will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA®; Version 19 or higher) System Organ Class (SOC) and preferred term, classified from verbatim terms. The incidence and percentage of subjects with at least one occurrence of a preferred term will be included, using the most severe grade. The number of events per preferred term will also be summarized. Causality (relationship to study drug [related/not related]) will be summarized separately.

TEAEs, SAEs, and AEs leading to withdrawal, dose modification, or treatment discontinuation will be listed by subject per SOC and preferred terms. Duration of AEs will be determined and included in listings, along with action taken and outcome.

Laboratory results will be summarized by visit, time point, dose, and dose regimen. The incidence of laboratory abnormalities will be summarized. The worst on-study grade after the first dose of study drug will be summarized. Results for variables that are not coded will be presented in the listings as below, within, and above the normal limits of the central laboratory.

Vital sign measurements and change from baseline will be summarized at each scheduled time point by cohort using descriptive statistics.

Arithmetic mean of parameters from triplicate ECG will be calculated first for each subject at each planned time point. Then summary statistics of ECG test parameters (mean of triplicate) and change from baseline to each post-dose time point will be calculated. Shift tables for ECG test result category change (normal, abnormal, clinically abnormal) from pre-dose to each post-

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dose time point showing number and percentage of subjects with movement between categories will be presented by treatment group. Frequency and percentage of subjects experiencing potential QTc prolongation (QTcF > 450) will be summarized at each time point by cohort.

Concomitant medications will be coded using WHO Drug Dictionary (WHO-DD March 2013, Type B2 or later) and the data will be summarized and presented in tables and listings.

11.4.3.2 Dose Selection Data

The evaluation of SYNT001 based on total IgG levels and responses on the PDAI total activity score from baseline will be summarized using descriptive statistics. Descriptive statistics will include mean, SD, coefficient of variation (CV), median, minimum, and maximum. The determination of dose and dosing duration of SYNT001 that achieves (i) total IgG level nadir decrease by \geq 60% and \leq 90% from baseline and (ii) a PDAI total activity score of \geq 50% reduction from baseline to allow further clinical development in subject with pemphigus (vulgaris or foliaceus).

11.4.4 Analysis of Secondary Endpoints

11.4.4.1 Pharmacokinetic Analysis

PK results for SYNT001 will be summarized by dose and dose regimen, visit and time point.

Descriptive statistics will be provided for the PK parameters including mean, SD, CV, median, minimum, and maximum.

For calculation of mean concentrations and generation of mean concentration-time profiles, all below the limit of quantification (BLQ) values will be set to zero except when an individual BLQ falls between 2 quantifiable values, in which case it will be omitted.

If there are values above the BLQ, but too sparse to allow full analysis, descriptive statistics will be performed on available values.

11.4.4.2 Pharmacodynamic Analysis

Disease activity marker results will be summarized by dose, dose regimen and visit. Descriptive statistics of PD will include mean, SD, median, minimum, and maximum.

11.4.4.3 Immunogenicity Analysis

Immunogenicity results will be summarized by cohort, visit and time point. Descriptive statistics will include mean, SD, CV, median, minimum, and maximum.

11.4.4.4 PDAI Data

PDAI results will be summarized by score (total activity score, total damage score), cohort, and visit. Descriptive statistics will include absolute change from baseline, and percent change from

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baseline. PDAI will also be summarized by disease severity category, mild (0 to 8), moderate (9 to 24), and severe (\geq 25).

11.4.5 Analysis of Exploratory Endpoints

11.4.5.1 Corticosteroid Use

The evaluation of corticosteroid use during the study will be summarized by dose, dose regimen and visit.

11.4.5.2 Health-Related Quality of Life Data

HR-QoL results from the ABQoL and Skindex-29 assessments will be summarized by dose, dose regimen, and visit.

11.4.5.3 Photography

The qualitative assessment of changes in appearance of skin and mucosal lesions as determined by photography presented by dose, dose regimen, and visit.

11.5 Interim Analysis

No interim analysis is planned.

12. STUDY MANAGEMENT

12.1 Regulatory and Ethical Considerations

12.1.1 Ethical Conduct

The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH E6 Tripartite Guideline (January 1997), and in general, be conducted in a manner consistent with the principles described in the Declaration of Helsinki. The Investigator will ensure that the conduct of the study complies with the basic principles of GCP as outlined in the current version of 21 CFR, subpart D, Part 312, "Responsibilities of Sponsors and Investigators", Part 50, "Protection of Human Subjects", and Part 56, "Institutional Review Boards".

12.1.2 Informed Consent

A signed informed consent form (ICF) in compliance with 21 CFR, Part 50.25(a) and Part 50.25(b) and the ICH guidelines, will be obtained from each subject before the subject is entered into the study and before any study screening procedure is performed that involves risk. The method of obtaining and documenting the informed consent will comply with ICH GCP and all applicable laws and regulations and will be subject to approval by the Sponsor.

The Investigator, or designee, is responsible for obtaining written informed consent from each subject (or the subject's legally authorized representative) participating in this study after a thorough and clear explanation of the objectives, procedures, anticipated benefits, and potential hazards of the study. In the case where the subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the subject has orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. The study site must retain the original ICF and a copy must be provided to the subject or to the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

The Sponsor, or designee, must review the signed ICF against any proposed deviations from a sample ICF the Sponsor has supplied to each site. The final IRB-approved document must be provided to the Sponsor for regulatory purposes.

The eCRF for this study contains a section for documenting informed subject consent, and this must be completed appropriately. Signed ICFs must remain in each subject's study file and must be available for verification by site monitors at any time. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated as necessary. All subjects (including those already being treated) should be informed of the new information, should be given a copy of the revised form, and should give their consent to continue in the study.

12.1.3 Subject Confidentiality and Privacy

As applicable, in accordance with the Health Insurance Portability and Accountability Act (HIPAA), and associated privacy regulations, a patient authorization to use personally

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identifiable health information may be required from each patient before research activities begin.

The Investigator must ensure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On eCRFs or other documents submitted to the Sponsor, subjects should be identified by an identification code and not by their names. The Investigator should keep a subject enrollment log showing codes, names, and addresses. The Investigator should maintain documents intended for storing onsite (eg, subjects' written consent forms) in strict confidence.

All study drugs, subject bodily fluids and tissue, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the Sponsor.

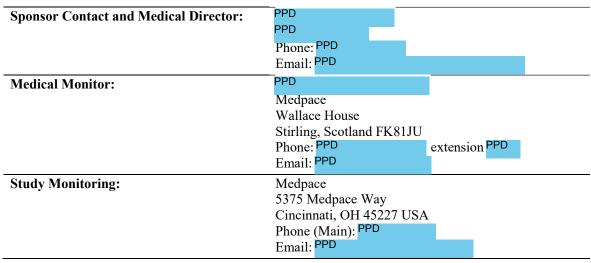
12.1.4 Future Use of Stored Specimens

Not all the tissue and blood components obtained during this study may be required for the tests that are part of the clinical trial. Available samples may be used for additional analyses and research. This research will help to understand disease subtypes, drug response, and AEs, and possibly identify new drug targets or biomarkers that predict subject response to treatment. The use of the samples for internal research will adhere to the guidelines defined by the FDA in "Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individual Identifiable" (issued 25 April 2006) and the European Medicines Agency "Reflection Paper on Pharmacogenetic Samples, Testing and Data Handling" (Doc. Ref. EMEA/CHMP/PGxWP/201914/2006; 15 November 2007). If a subject requests destruction of their tissue and blood samples and the samples have not yet been de-identified, the Sponsor will destroy the samples as described in the FDA guidance. The Sponsor will notify the Investigator in writing that the samples have been destroyed.

12.2 Study Administration

The study administration structure is provided in Table 9.





12.2.1 Institutional Review Board Approval

This study is being conducted under US IND 132727. This protocol (and any modifications) and appropriate consent procedures must be reviewed and approved by the site-specific IRB before the study is initiated. The IRB must operate in accordance with the current federal or local regulations. The Investigator will send a letter or certificate of IRB approval to the Sponsor (or designee) before subject enrollment and whenever subsequent modifications to the protocol are made.

12.2.2 Data Handling and Record Keeping

All data will be entered in a validated electronic data capture system using single data entry. Standard procedures (including following data review guidelines, manual clinical review based on subject profiles, computerized validation to produce queries, and maintenance of an audit file, which includes all database modifications) will be followed to ensure accurate data. Clinical personnel will review all data listings for outliers, data inconsistencies, and spelling errors.

12.2.3 Data Protection

The Investigator agrees that all information received from the Sponsor, including but not limited to the IB, this protocol, eCRFs, the INDs, and any other study information remain the sole and exclusive property of the Sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) or otherwise into the public domain without prior written consent from the Sponsor.

12.2.4 Study Site Regulatory Documentation

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should

be classified into 2 separate categories as follows: (1) Investigator's study file and (2) subject clinical source documents (see Section 12.2.5).

The Investigator's study file will contain the protocol and protocol amendments, eCRFs, query forms, IRB and governmental approval with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Subject clinical source documents (usually predefined by the project to record key efficacy and safety parameters independent of the eCRFs) may include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalogram, X-ray, pathology and special assessment reports, signed ICFs, consultant letters, and subject screening and enrollment logs. The Investigator must keep these two categories of documents on file for at least 2 years following the marketing application approval date for the study treatment and for the indication being investigated or for 2 years after the development program is discontinued and the FDA notified. After that period, the documents may be destroyed subject to local regulations with prior written permission from the Sponsor. If the Investigator wants to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

If the Investigator cannot guarantee the archiving requirement at the study site for any or all of the documents, special arrangements must be made between the Investigator and the Sponsor to store these in a sealed container outside of the study site so that they can be returned sealed to the Investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the study site.

12.2.5 Subject Clinical Source Documents and Background Data

Investigators must maintain adequate and accurate source documents on which the eCRFs for each subject are based. They are separate and distinct from the eCRFs.

These records include detailed notes on the following:

- Medical history
- Informed consent
- HIPAA authorization, if applicable (either contained in the ICF or presented to the subject candidate as a standalone document)
- Description of the complete consenting process
- The basic identifying information that linked the subject's medical record with the eCRFs
- The results of all diagnostic tests performed, diagnoses made, therapy provided, and any other data on the condition of the subject
- The medical condition of the subject during their involvement in the study
- All AEs
- The subject's exposure to the study medication
- The subject's exposure to any concomitant therapy
- All relevant observations and data on the condition of the subject throughout the trial
- Justification for all entries in the subject's eCRF

A subject log of all potentially eligible subjects considered, but not consented, for obvious deviations from the entry criteria, will be kept at each site. The log will contain subjects' initials, diagnosis, eligibility, or, if not eligible, reason for not consenting. All consented subjects will be logged, regardless of whether they ultimately enroll.

Upon request, the Investigator will supply the Sponsor with any required background data from the study documentation or clinic records. This is particularly important when eCRFs are illegible or when errors in data transcription are suspected. In case of special problems or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

12.2.6 Electronic Case Report Forms

Clinical trial data for this study will be captured on eCRF designed for computer processing and analysis. This computerized system will be validated and compliant with 21 CFR Part 11, as described in the FDA guidance "Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11 – Questions and Answers." If corrections are made after review and sign-off by the Investigator, he/she must be aware of the changes and provide written acknowledgement. There will also be an electronic audit trail. Corrections on paper CRFs must be initialed and dated by the person making the change. The Investigator agrees to provide all information requested on the eCRF in an accurate manner using instructions provided. The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the eCRF and in all required reports.

An eCRF is required to be submitted for every subject who receives any amount of study drug. This includes submission of retrievable data on subjects who withdraw before completion of the study. Prior to submission, eCRFs must be reviewed for completeness and accuracy, and signed and dated where indicated, by the Investigator or designee. If a subject stops treatment or terminates from the study, the dates and reasons must be noted on the eCRF.

12.3 Clinical Monitoring, Audits, and Inspections

The Investigator and study staff are responsible for maintaining a comprehensive and accurate filing system of all study-related documentation that will be suitable for inspection for routine monitoring, audit, or inspection at any time by the Sponsor (or designee) and/or a regulatory authority.

12.3.1 Clinical Monitoring

During the clinical study, it is understood that the responsible Sponsor site monitor or designee (eg, contract research organization [CRO]) will contact and visit the study site at regular intervals for routine monitoring of various records. Routine monitoring activities will be conducted to verify adherence to the protocol, completeness, consistency and accuracy of the data, and to review study source documents and drug accountability records. Regular review of the eCRFs for completeness, clarity, and to cross-check against source documents is required to

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monitor the progress of the study. Data will be reviewed and verified against the source documents (eg, original medical records and laboratory results) to ensure validity.

The Investigator will provide the Sponsor or designee with full access to all source data (including laboratory tests) and provide administrative support if requested. The Investigator (or designee) must agree to cooperate with the site monitor to ensure that any problems detected during these monitoring visits are resolved.

Site-specific study procedures, such data-recording and handling of the data, may be assessed during the study by a Clinical Quality Assurance representative(s) authorized by the Sponsor. Further, this designee, as well as the site monitor, will be permitted to inspect the study documents (study protocol, eCRFs, study drug accountability, original study-relevant medical records) to ensure that the study is conducted in compliance with the protocol.

During these visits, all representatives of the Sponsor will be responsible for ensuring data integrity and subject confidentiality is protected.

12.3.2 Audits and Inspections

Clinical site and study audits will be conducted as necessary to assure the validity of the study data. The Sponsor (or designee) may perform a quality assurance audit to ensure compliance with GCP, this protocol, and all applicable regulatory requirements. The Investigator should ensure that study documents (protocol, eCRFs, study drug record-keeping, original study-relevant medical records) are made available to the Sponsor (or designee) for examination. All subject data will be treated as confidential.

A regulatory authority, after appropriate notification, may also wish to conduct an inspection during the study or even after its completion. If a regulatory authority requests an inspection, the Investigator must immediately inform the Sponsor.

12.4 Changes to the Protocol

Protocol modifications to ongoing studies must be made only after consultation between a Sponsor representative and the Investigator. Protocol modifications will be prepared, reviewed, and approved by Sponsor representatives.

All protocol modifications must be submitted to the IRB for information and approval in accordance with local requirements, and to regulatory agencies, if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study subjects, or when the change involves only logistical or administrative aspects of the trial (eg, change in site monitor, change of telephone number).

12.5 Study Discontinuation and Closure

The Sponsor has the right to terminate the study at any time. In terminating the study, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the subjects' interests.

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13. PUBLICATION AND DATA SHARING POLICY

The results of this study may be published or presented at scientific meetings. The Investigator agrees that any manuscript or abstract they author may be published only after receiving written permission from the Sponsor.

If the Sponsor coordinates a publication or presentation of study results from all study sites, the participation of Investigator or other representatives of study site as a named author shall be determined in accordance with the Sponsor's policy and generally accepted standards for authorship as developed by the International Committee of Medical Journal Editors (ICMJE) and in accordance with Good Publication Practices.

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APPENDIX 1. NCI CTCAE, VERSION 4.03

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Common Terminology Criteria for Adverse Events (CTCAE)

Version 4.0

Published: May 28, 2009 (v4.03: June 14, 2010)

U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health National Cancer Institute

Common Terminology Criteria for Adverse Events v4.0 (CTCAE) Publish Date: May 28, 2009

Quick Reference

The NCI Common Terminology Criteria Adverse Events is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

SOC

System Organ Class, the highest level of the MedDRA hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e. SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

CTCAE Terms

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disea temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analysis Each CTCAE v4.0 term is a MedDRA LLT (Lowest Level Term).

Definitions

A brief definition is provided to clarify the meaning of each AE term.

Grades

displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic telephone, managing money, etc. observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; medications, and not bedridden. limiting age-appropriate instrumental ADL*.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

A Semi-colon indicates 'or' within the description of the grade.

A single dash (-) indicates a grade is not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than e options for Grade selection.

Grade refers to the severity of the AE. The CTCAE

Grade 5 (Death) is not appropriate for some AEs
displays Grades 1 through 5 with unique clinical
and therefore is not an option.

ctivities of Daily Living (ADL)

Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the

Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking

[†] CTCAE v4.0 incorporates certain elements of the MeduRA terminology. For further details on MedDRA refer to the MedDRA MSSO Web site (http://www.meddramsso.com).

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	В	lood and lymphatic system	em disorders		
			Grade		
Adverse Event	1	2	3	4	5
Anemia	Hemoglobin (Hgb) <lln -="" 10.0<br="">g/dL; <lln -="" -<br="" 6.2="" <lln="" l;="" mmol="">100 g/L</lln></lln>	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
	ed by an reduction in the amount of palpitations of the heart, soft syst	•	• • •	ay include pallor of the skin and m	nucous
Bone marrow hypocellular	Mildly hypocellular or <=25% reduction from normal cellularity for age	Moderately hypocellular or >25 - <50% reduction from normal cellularity for age	Severely hypocellular or >50 - <=75% reduction cellularity from normal for age	Aplastic persistent for longer than 2 weeks	Death
Definition: A disorder characteriz	ed by the inability of the bone mar	row to produce hematopoietic ele	ments.		
Disseminated intravascular coagulation	-	Laboratory findings with no bleeding	Laboratory findings and bleeding	Life-threatening consequences; urgent intervention indicated	Death
	ed by systemic pathological activa s depleted of platelets and coagula	-	which results in clot formation thro	oughout the body. There is an incr	ease in the
Febrile neutropenia	-	-	ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour.	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz degrees F) for more than one ho	ed by an ANC <1000/mm3 and a sur.	single temperature of >38.3 degre	es C (101 degrees F) or a sustaine	ed temperature of >=38 degrees 0	C (100.4
Hemolysis	Laboratory evidence of hemolysis only (e.g., direct antiglobulin test; DAT; Coombs'; schistocytes; decreased haptoglobin)	Evidence of hemolysis and >=2 gm decrease in hemoglobin.	Transfusion or medical intervention indicated (e.g., steroids)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by laboratory test results that in	ndicate widespread erythrocyte ce	Il membrane destruction.	I	
Hemolytic uremic syndrome	Evidence of RBC destruction (schistocytosis) without clinical consequences	-	Laboratory findings with clinical consequences (e.g., renal insufficiency, petechiae)	Life-threatening consequences, (e.g., CNS hemorrhage or thrombosis/embolism or renal failure)	Death
Definition: A disorder characteriz	ed by a form of thrombotic microa	ngiopathy with renal failure, hemo	lytic anemia, and severe thromboo	ytopenia.	
_eukocytosis	-	-	>100,000/mm3	Clinical manifestations of leucostasis; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by laboratory test results that ir	ndicate an increased number of w	nite blood cells in the blood.		
_ymph node pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by a sensation of marked disco	omfort in a lymph node.			
Spleen disorder	Incidental findings (e.g., Howell- Jolly bodies); mild degree of thrombocytosis and leukocytosis	Prophylactic antibiotics indicated	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder of the splee	en.				
Thrombotic thrombocytopenic ourpura	Evidence of RBC destruction (schistocytosis) without clinical consequences	-	Laboratory findings with clinical consequences (e.g., renal insufficiency, petechiae)	Life-threatening consequences, (e.g., CNS hemorrhage or thrombosis/embolism or renal failure)	Death
	ed by the presence of microangion al disturbances. It is an acute or s	•	cytopenic purpura, fever, renal abr	normalities and neurological abnor	malities suc
Blood and lymphatic system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic	Moderate; minimal, local or noninvasive intervention	Severe or medically significant but not immediately life-	Life-threatening consequences; urgent intervention indicated	Death
	observations only; intervention not indicated	indicated; limiting age- appropriate instrumental ADL	threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL		

Cardiac disorders								
		T	Grade	Г	1			
Adverse Event	1	2	3	4	5			
Acute coronary syndrome	-	Symptomatic, progressive angina; cardiac enzymes normal; hemodynamically stable	Symptomatic, unstable angina and/or acute myocardial infarction, cardiac enzymes abnormal, hemodynamically stable	Symptomatic, unstable angina and/or acute myocardial infarction, cardiac enzymes abnormal, hemodynamically unstable	Death			
		•	dium secondary to coronary artery	disease. The clinical presentation	covers a			
	unstable angina to myocardial inf		I		I			
Aortic valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis by imaging	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death			
Definition: A disorder characteriz	ed by a defect in aortic valve func	tion or structure.	T	T				
Asystole	Periods of asystole; non-urgent medical management indicated	-	-	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteriz	ed by a dysrhythmia without cardi	ac electrical activity. Typically, this	is accompanied by cessation of the	ne pumping function of the heart.				
Atrial fibrillation	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker), or ablation	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteriz originates above the ventricles.	ed by a dysrhythmia without disce	rnible P waves and an irregular ve	entricular response due to multiple	reentry circuits. The rhythm distur	bance			
Atrial flutter	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker), or ablation	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteriz atria.	ed by a dysrhythmia with organize	ed rhythmic atrial contractions with	a rate of 200-300 beats per minut	e. The rhythm disturbance origina	tes in the			
Atrioventricular block complete	-	Non-urgent intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteriz	ed by a dysrhythmia with complet	· e failure of atrial electrical impulse	conduction through the AV node t	o the ventricles.				
Atrioventricular block first degree	Asymptomatic, intervention not indicated	Non-urgent intervention indicated	-	-	-			
	ted by a dysrhythmia with a delay interval greater than 200 milliseco	•	tion of an electrical impulse throug	gh the atrioventricular (AV) node be	eyond 0.			
Cardiac arrest	-	-	-	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteriz	ed by cessation of the pumping fu	nction of the heart.						
Chest pain - cardiac	Mild pain	Moderate pain; limiting instrumental ADL	Pain at rest; limiting self care ADL	-	-			
Definition: A disorder characteriz	ed by substernal discomfort due to	o insufficient myocardial oxygenati	on.					
Conduction disorder	Mild symptoms; intervention not indicated	Moderate symptoms	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteriz	ed by pathological irregularities in	the cardiac conduction system.	T					
Constrictive pericarditis	-	-	Symptomatic heart failure or other cardiac symptoms, responsive to intervention	Refractory heart failure or other poorly controlled cardiac symptoms	Death			
	1	cardial sact these fibrotic changes	i mpede normal myocardial function	1	e action.			
Definition: A disorder characteriz	ed by a thickened and fibrotic peri	odraidi odo, triodo librotio oridrigos						

Cardiac disorders								
			Grade					
Adverse Event	1	2	3	4	5			
Left ventricular systolic dysfunction	-	-	Symptomatic due to drop in ejection fraction responsive to intervention	Refractory or poorly controlled heart failure due to drop in ejection fraction; intervention such as ventricular assist device, intravenous vasopressor support, or heart transplant indicated	Death			
	ed by failure of the left ventricle to nea, orthopnea, and other signs ar		e an increase in distending pressurestion and edema.	e and in end-diastolic volume. Clin	ical			
Mitral valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis by imaging	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death			
Definition: A disorder characteriz	ed by a defect in mitral valve func	tion or structure.						
Mobitz (type) II atrioventricular olock	Asymptomatic, intervention not indicated	Symptomatic; medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening consequences; urgent intervention indicated	Death			
	ed by a dysrhythmia with relatively atrioventricular (AV) node to the ve	•	block of an atrial impulse. This is t	he result of intermittent failure of a	trial electi			
Mobitz type I	Asymptomatic, intervention not indicated	Symptomatic; medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening consequences; urgent intervention indicated	Death			
	ed by a dysrhythmia with a progre on through the atrioventricular (AV		rior to the blocking of an atrial impu	ilse. This is the result of intermitter	nt failure o			
Myocardial infarction	-	Asymptomatic and cardiac enzymes minimally abnormal and no evidence of ischemic ECG changes	Severe symptoms; cardiac enzymes abnormal; hemodynamically stable; ECG changes consistent with infarction	Life-threatening consequences; hemodynamically unstable	Death			
Definition: A disorder characteriz	ed by gross necrosis of the myoca	ardium; this is due to an interruption	on of blood supply to the area.					
Myocarditis	Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	Death			
Definition: A disorder characteriz	ed by inflammation of the muscle	tissue of the heart.						
Palpitations	Mild symptoms; intervention not indicated	Intervention indicated	-	-	-			
Definition: A disorder characteriz	ed by an unpleasant sensation of	irregular and/or forceful beating o	f the heart.	_				
Paroxysmal atrial tachycardia	Asymptomatic, intervention not indicated	Symptomatic; medical management indicated	IV medication indicated	Life-threatening consequences; incompletely controlled medically; cardioversion indicated	Death			
Definition: A disorder characteriz originates in the atria.	ed by a dysrhythmia with abrupt o	nset and sudden termination of a	trial contractions with a rate of 150-	-250 beats per minute. The rhythm	disturba			
Pericardial effusion	-	Asymptomatic effusion size small to moderate	Effusion with physiologic consequences	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteriz	ed by fluid collection within the pe	ricardial sac, usually due to inflam	nmation.					
	-	-	-	Life-threatening consequences; urgent intervention indicated	Death			
Pericardial tamponade								
·	l ed by an increase in intrapericardi	al pressure due to the collection of	of blood or fluid in the pericardium.					

		Cardiac disorde	ers		
			Grade		
Adverse Event	1	2	3	4	5
Pulmonary valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis by imaging	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death
Definition: A disorder characteriz	ed by a defect in pulmonary valve	function or structure.	<u> </u>		,
Restrictive cardiomyopathy	-	-	Symptomatic heart failure or other cardiac symptoms, responsive to intervention	Refractory heart failure or other poorly controlled cardiac symptoms	Death
	ted by an inability of the ventricles	1	1 '	1	1
Right ventricular dysfunction	Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Severe symptoms, associated with hypoxemia, right heart failure; oxygen indicated	Life-threatening consequences; urgent intervention indicated (e.g., ventricular assist device); heart transplant indicated	Death
	ed by impairment of right ventricul	ar function associated with low eje	ection fraction and a decrease in m T	notility of the right ventricular wall.	
Sick sinus syndrome	Asymptomatic, intervention not indicated	Non-urgent intervention indicated	Severe, medically significant; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	ed by a dysrhythmia with alternation		1	1	
Sinus bradycardia	Asymptomatic, intervention not indicated	Symptomatic, medical intervention indicated	Severe, medically significant, medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by a dysrhythmia with a heart r	ate less than 60 beats per minute	that originates in the sinus node.	T	
Sinus tachycardia	Asymptomatic, intervention not indicated	Symptomatic; non-urgent medical intervention indicated	Urgent medical intervention indicated	-	-
Definition: A disorder characterize	ed by a dysrhythmia with a heart r	ate greater than 100 beats per mi	nute that originates in the sinus no	de.	
Supraventricular tachycardia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by a dysrhythmia with a heart r	ate greater than 100 beats per mi	nute that originates above the ven	tricles.	
Tricuspid valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death
Definition: A disorder characteriz	red by a defect in tricuspid valve fu	nction or structure.	T	T	
Ventricular arrhythmia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by a dysrhythmia that originate	s in the ventricles.			
Ventricular fibrillation	-	-	-	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Definition: A disorder characteriz ventricles.	ed by a dysrhythmia without disce	rnible QRS complexes due to rapi	d repetitive excitation of myocardi	al fibers without coordinated contr	action of the
Ventricular tachycardia	-	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by a dysrhythmia with a heart r	ate greater than 100 beats per mi	nute that originates distal to the bu	ındle of His.	
Wolff-Parkinson-White syndrome	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with procedure	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by the presence of an accesso	ry conductive pathway between th	e atria and the ventricles that caus	ses premature ventricular activation	n.
Cardiac disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

	Congenital, familial and genetic disorders							
	Grade							
Adverse Event	1	2	3	4	5			
Congenital, familial and genetic	Asymptomatic or mild	Moderate; minimal, local or	Severe or medically significant	Life-threatening consequences;	Death			
disorders - Other, specify	symptoms; clinical or diagnostic	noninvasive intervention	but not immediately life-	urgent intervention indicated				
	observations only; intervention	indicated; limiting age-	threatening; hospitalization or					
	not indicated	appropriate instrumental ADL	prolongation of existing					
			hospitalization indicated;					
i			disabling; limiting self care ADL					

		Ear and labyrinth dis	sorders		
		·	Grade		
Adverse Event	1	2	3	4	5
Ear pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by a sensation of marked disco	mfort in the ear.			
External ear inflammation	External otitis with erythema or dry desquamation	External otitis with moist desquamation, edema, enhanced cerumen or discharge; tympanic membrane perforation; tympanostomy	External otitis with mastoiditis; stenosis or osteomyelitis; necrosis of soft tissue or bone	Urgent operative intervention indicated	Death
Definition: A disorder characteriz	ed by inflammation, swelling and r	edness to the outer ear and ear c	anal.	•	
External ear pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by a sensation of marked disco	mfort in the external ear region.			
Hearing impaired	Adults enrolled on a Monitoring Program (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift of 15 - 25 dB averaged at 2 contiguous test frequencies in at least one ear. Adults not enrolled in Monitoring Program: subjective change in hearing in the absence of documented hearing loss. Pediatric (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift >20 dB at 8 kHz in at least one ear.	Adults enrolled in Monitoring Program (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift of >25 dB averaged at 2 contiguous test frequencies in at least one ear. Adults not enrolled in Monitoring Program: hearing loss but hearing aid or intervention not indicated; limiting instrumental ADL. Pediatric (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift >20 dB at 4 kHz and above in at least one ear.	Adults enrolled in Monitoring Program (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift of >25 dB averaged at 3 contiguous test frequencies in at least one ear; therapeutic intervention indicated. Adults not enrolled in Monitoring Program: hearing loss with hearing aid or intervention indicated; limiting self care ADL. Pediatric (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): hearing loss sufficient to indicate therapeutic intervention, including hearing	Adults: Decrease in hearing to profound bilateral loss (absolute threshold >80 dB HL at 2 kHz and above); non-servicable hearing. Pediatric: Audiologic indication for cochlear implant and additional speech-language related services indicated.	-
	ted by partial or complete loss of th	ne ability to detect or understand s	aids; threshold shift >20 dB at 3 kHz and above in at least one ear; additional speech-language related services indicated.		
Middle ear inflammation	Serous otitis	Serous otitis, medical	Mastoiditis; necrosis of canal	Life-threatening consequences;	Death
D 6 ''' A 1'' I I I I I I I I I		intervention indicated	soft tissue or bone	urgent intervention indicated	l
Tinnitus	mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
	red by noise in the ears, such as rin				
Vertigo	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characteriz vertigo).	eed by a sensation as if the externa	1	1	। he himself were revolving in space	i e (subjective
Vestibular disorder	-	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by dizziness, imbalance, nause	ea, and vision problems.	I	r	1
Ear and labyrinth disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

		Endocrine disord	lers		
			Grade		
Adverse Event	1	2	3	4	5
Adrenal insufficiency	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
	rs when the adrenal cortex does not ison's disease or primary adrenal in:	·	cortisol and in some cases, the ho	ormone aldosterone. It may be due	to a disorde
Cushingoid	Mild symptoms; intervention not indicated	intervention indicated	Severe symptoms, medical intervention or hospitalization indicated	-	-
Definition: A disorder character osteoporosis, usually due to ex	rized by signs and symptoms that re cogenous corticosteroids.	semble Cushing's disease or sync	lrome: buffalo hump obesity, striat	tions, adiposity, hypertension, diab	etes, and
Delayed puberty	-	No breast development by age 13 yrs for females; testes volume of <3 cc or no Tanner Stage 2 development by age 14.5 yrs for males	No breast development by age 14 yrs for females; no increase in testes volume or no Tanner Stage 2 by age 16 yrs for males; hormone replacement indicated	-	-
Definition: A disorder character	rized by unusually late sexual maturi	ty.	,	•	•
Growth accelerated	-	>= +2 SD (standard deviation) above mid parental height or target height	-	-	-
Definition: A disorder character	rized by greater growth than expecte	d for age.		1	
Hyperparathyroidism	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder character the blood).	rized by an increase in production of	parathyroid hormone by the para	thyroid glands. This results in hype	ercalcemia (abnormally high levels	of calcium i
Hyperthyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder character	rized by excessive levels of thyroid h	ormone in the body. Common car	uses include an overactive thyroid	gland or thyroid hormone overdos	e.
Hypoparathyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; medical intervention or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder character	rized by a decrease in production of	parathyroid hormone by the parat	hyroid glands.		•
Hypothyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid replacement indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
	rized by a decrease in production of		and.	1	
Precocious puberty	Physical signs of puberty with no biochemical markers for females <8 years and males <9 years	Physical signs and biochemical markers of puberty for females <8 years and males <9 years	-	-	-
Definition: A disorder character 9 for boys.	rized by unusually early developmen	t of secondary sexual features; th	e onset of sexual maturation begir	ns usually before age 8 for girls an	d before age
Virilization	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder character	rized by inappropriate masculinization	n occurring in a female or prepub	ertal male.		
Endocrine disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

		Eye dis	sorders		
			Grade		
Adverse Event	1	2	3	4	5
Blurred vision	Intervention not indicated	Symptomatic; limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder charact	erized by visual perception of u		<u> </u>	<u> </u>	ĺ
Cataract	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; moderate decrease in visual acuity (20/40 or better)	Symptomatic with marked decrease in visual acuity (worse than 20/40 but better than 20/200); operative intervention indicated (e.g.,	Blindness (20/200 or worse) in the affected eye	-
	<u> </u>		cataract surgery)		
Definition: A disorder charact untreated.	erized by partial or complete op	acity of the crystalline lens of c	one or both eyes. This results in	n a decrease in visual acuity an	d eventual blindness if
Conjunctivitis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; topical intervention indicated (e.g., antibiotics); limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder charact	erized by inflammation, swelling	and redness to the conjunctive	a of the eye.	1	I
Corneal ulcer	-	Symptomatic; medical intervention indicated (e.g., topical agents); limiting instrumental ADL	Limiting self care ADL; declining vision (worse than 20/40 but better than 20/200)	Perforation or blindness (20/200 or worse) in the affected eye	-
Definition: A disorder charact	erized by an area of epithelial ti	ssue loss on the surface of the	cornea. It is associated with in	flammatory cells in the cornea	and anterior chamber.
Dry eye	Asymptomatic; clinical or diagnostic observations only; mild symptoms relieved by lubricants	Symptomatic; multiple agents indicated; limiting instrumental ADL	Decrease in visual acuity (<20/40); limiting self care ADL	-	-
Definition: A disorder charact	erized by dryness of the cornea	and conjunctiva.			
Extraocular muscle paresis	Asymptomatic; clinical or diagnostic observations only	Symptomatic; limiting instrumental ADL	Limiting self care ADL; disabling	-	-
Definition: A disorder charact	erized by incomplete paralysis	of an extraocular muscle.	T	T	
Eye pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder charact	erized by a sensation of marked	d discomfort in the eye.		I	1
Eyelid function disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; nonoperative intervention indicated; limiting instrumental ADL	Limiting self care ADL; operative intervention indicated	-	-
Definition: A disorder charact	erized by impaired eyelid function	on.	T	T	T
Flashing lights	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder charact	erized by a sudden or brief burs	st of light.			
Floaters	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder charact	erized by an individual seeing s	pots before their eyes. The spo	ots are shadows of opaque cell	fragments in the vitreous humo	or or lens.
Glaucoma	Elevated intraocular pressure (EIOP) with single topical agent for intervention; no visual field deficit	EIOP causing early visual field deficits; multiple topical or oral agents indicated; limiting instrumental ADL	EIOP causing marked visual field deficits (e.g., involving both superior and inferior visual fields); operative intervention indicated; limiting self care ADL	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder charact	erized by an increase in pressu	· re in the eyeball due to obstruc	tion of the aqueous humor out	flow.	:
Keratitis	-	Symptomatic; medical intervention indicated (e.g., topical agents); limiting instrumental ADL	Decline in vision (worse than 20/40 but better than 20/200); limiting self care ADL	Perforation or blindness (20/200 or worse) in the affected eye	-
Definition: A disorder charact	erized by inflammation to the co	ornea of the eye.	T	T	
Night blindness	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder charact	erized by an inability to see clea	arly in dim light.			

		Eye dis	sorders		
			Grade		
Adverse Event	1	2	3	4	5
Optic nerve disorder	Asymptomatic; clinical or diagnostic observations only	Limiting vision of the affected eye (20/40 or better)	Limiting vision in the affected eye (worse than 20/40 but better than 20/200)	Blindness (20/200 or worse) in the affected eye	-
	erized by involvement of the op	1	ĺ		1
Papilledema	Asymptomatic; no visual field defects	vision; visual field defect present sparing the central 20 degrees	Marked visual field defect (worse than 20/40 but better than 20/200)	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder charact	erized by swelling around the o	ptic disc. T	<u> </u>	<u> </u>	
Photophobia	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder charact	erized by fear and avoidance of	f light.			
Retinal detachment	Asymptomatic	Exudative and visual acuity 20/40 or better	Rhegmatogenous or exudative detachment; operative intervention indicated; decline in vision (worse than 20/40 but better than 20/200)	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder charact	erized by the separation of the	inner retina layers from the und	lerlying pigment epithelium.		
Retinal tear	-	Laser therapy or pneumopexy indicated	Vitroretinal surgical repair indicated	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder charact	erized by a small laceration of t	he retina, this occurs when the	vitreous separates from the re	tina. Symptoms include flashes	s and floaters.
Retinal vascular disorder	-	Topical medication indicated	Intravitreal medication; operative intervention indicated	-	-
Definition: A disorder charact	erized by pathological retinal bl	ood vessels that adversely affe	cts vision.		
Retinopathy	Asymptomatic; clinical or diagnostic observations only	Symptomatic with moderate decrease in visual acuity (20/40 or better); limiting instrumental ADL	Symptomatic with marked decrease in visual acuity (worse than 20/40); disabling; limiting self care ADL	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder involvin	g the retina.				
Scleral disorder	Asymptomatic; clinical or diagnostic observations only	Symptomatic, limiting instrumental ADL; moderate decrease in visual acuity (20/40 or better)	Symptomatic, limiting self care ADL; marked decrease in visual acuity (worse than 20/40)	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder charact	erized by involvement of the so	lera of the eye.	Τ	Τ	I
Uveitis	Asymptomatic; clinical or diagnostic observations only	•	Posterior or pan-uveitis	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder charact	erized by inflammation to the uv	vea of the eye.	i -	i -	1
Vitreous hemorrhage	Asymptomatic or mild symptoms; clinical or diagnostic observations only	Symptomatic; limiting instrumental ADL	Limiting self care ADL; vitrectomy indicated	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder charact	erized by blood extravasation in	nto the vitreous humor.	T	T	T
Watering eyes	Intervention not indicated	Intervention indicated	Operative intervention indicated	-	-
Definition: A disorder of exce	ssive tearing in the eyes; it can	be caused by overproduction of	of tears or impaired drainage of	the tear duct.	
Eye disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately sight- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye	-

		Gastrointestinal dis	orders		
			Grade		
Adverse Event	1	2	3	4	5
Abdominal distension	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe discomfort; limiting self care ADL	-	-
Definition: A disorder characte	erized by swelling of the abdomen.				1
Abdominal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characte	erized by a sensation of marked disco	omfort in the abdominal region.	T	Г	1
Anal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	erized by an abnormal communication	between the opening in the anal	canal to the perianal skin.		
Anal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	erized by bleeding from the anal region	on.	T		1
Anal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	erized by inflammation of the mucous	membrane of the anus.	Ι	<u> </u>	1
Anal necrosis	-	a in the engl region	TPN or hospitalization indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
	erized by a necrotic process occurring		Sovere pain: limiting self core		
Anal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
	erized by a sensation of marked disco		0 / "	Let up a control of the control of t	Б. "
Anal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Symptomatic and severely altered GI function; non- emergent operative intervention indicated; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characte	erized by a narrowing of the lumen of	the anal canal.			
Anal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characte	erized by a circumscribed, inflammato	ory and necrotic erosive lesion on t	the mucosal surface of the anal ca	nal.	
Ascites	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characte	erized by accumulation of serous or h	emorrhagic fluid in the peritoneal	cavity.	•	•
Bloating	No change in bowel function or oral intake	Symptomatic, decreased oral intake; change in bowel function	-	-	-
Definition: A disorder characte	rized by subject-reported feeling of ι	uncomfortable fullness of the abdo	men.	•	•
Cecal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	erized by bleeding from the cecum.			•	•
Cheilitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; intervention indicated	-	-
		1	I .	ı	I

Gastrointestinal disorders Grade						
		Ι .			١ .	
Adverse Event	1	2	3	4		
Colitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characte	rized by inflammation of the colon.					
Colonic fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; bowel rest, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characte	rized by an abnormal communication	between the large intestine and	another organ or anatomic site.			
Colonic hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characte	rized by bleeding from the colon.	T	T	Г		
Colonic obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated rized by blockage of the normal flow	Symptomatic; altered GI function	Hospitalization indicated; elective operative intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death	
	Tized by blockage of the normal flow				D41-	
Colonic perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	
	rized by a rupture in the colonic wall.				ı	
Colonic stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death	
Definition: A disorder characte	rized by a narrowing of the lumen of	the colon.	•	•		
Colonic ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death	
Definition: A disorder characte	rized by a circumscribed, inflammato	ory and necrotic erosive lesion on	the mucosal surface of the colon.			
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL	Obstipation with manual evacuation indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characte	rized by irregular and infrequent or d	ifficult evacuation of the bowels.				
Dental caries	One or more dental caries, not involving the root	Dental caries involving the root	Dental caries resulting in pulpitis or periapical abscess or resulting in tooth loss	-	-	
Definition: A disorder characte	rized by the decay of a tooth, in whice	th it becomes softened, discolored	and/or porous.			
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characte	rized by frequent and watery bowel r	movements.				
Dry mouth	Symptomatic (e.g., dry or thick	Moderate symptoms; oral intake	Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva <0.1 ml/min	-	-	

Gastrointestinal disorders						
			Grade			
Adverse Event	1	2	3	4	5	
Duodenal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered Gl function	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characte	erized by an abnormal communication	n between the duodenum and and	other organ or anatomic site.			
Duodenal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characte	erized by bleeding from the duodenur	n.				
Duodenal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Hospitalization or elective operative intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death	
Definition: A disorder characte	erized by blockage of the normal flow	of stomach contents through the	duodenum.			
Duodenal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death	
Definition: A disorder characte	erized by a rupture in the duodenal w	all.	1	1		
Duodenal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death	
Definition: A disorder characte	erized by a narrowing of the lumen of	the duodenum.				
Duodenal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death	
Definition: A disorder characte	erized by a circumscribed, inflammate	ory and necrotic erosive lesion on	the mucosal surface of the duoder	nal wall.		
Dyspepsia	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; surgical intervention indicated	-	-	
Definition: A disorder characto heartburn, nausea and vomiti	erized by an uncomfortable, often pai	nful feeling in the stomach, resulti	ing from impaired digestion. Sympt	oms include burning stomach, blo	ating,	
Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing	Severely altered eating/swallowing; tube feeding or TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characte	erized by difficulty in swallowing.	1	1	1	'	
Enterocolitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe or persistent abdominal pain; fever; ileus; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characte	erized by inflammation of the small ar	nd large intestines.				
Enterovesical fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; noninvasive intervention indicated	Severe, medically significant; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characte	erized by an abnormal communication	n between the urinary bladder and	d the intestine.			
Esophageal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characte	erized by an abnormal communication	n between the esophagus and an	other organ or anatomic site.	•	•	
Esophageal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical	Transfusion, radiologic,	Life-threatening consequences;	Death	

Gastrointestinal disorders						
			Grade			
Adverse Event	1	2	3	4	5	
Esophageal necrosis	-	-	Inability to aliment adequately by GI tract; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death	
Definition: A disorder characte	erized by a necrotic process occurring	g in the esophageal wall.				
Esophageal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characte	erized by blockage of the normal flow	of the contents in the esophagus	i. T	T		
Esophageal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-	
Definition: A disorder characte	erized by a sensation of marked disco	omfort in the esophageal region.				
Esophageal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death	
	erized by a rupture in the wall of the e	1	1	<u> </u>		
Esophageal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death	
Definition: A disorder characte	erized by a narrowing of the lumen of	the esophagus.				
Esophageal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death	
Definition: A disorder characte	erized by a circumscribed, inflammato	ory and necrotic erosive lesion on	the mucosal surface of the esopha	geal wall.		
Esophageal varices hemorrhage	-	Self-limited; intervention not indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characte	erized by bleeding from esophageal v	rarices.				
Esophagitis Definition: A disorder character	Asymptomatic; clinical or diagnostic observations only; intervention not indicated erized by inflammation of the esophar	Symptomatic; altered eating/swallowing; oral supplements indicated	Severely altered eating/swallowing; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death	
Fecal incontinence	Occasional use of pads required		Severe symptoms; elective	-	-	
			operative intervention indicated			
Definition: A disorder characte	erized by inability to control the escap	e of stool from the rectum.				
Flatulence	Mild symptoms; intervention not indicated	psychosocial sequelae	-	-	-	
	erized by a state of excessive gas in t		1			
Gastric fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; bowel rest; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death	
Definition: A disorder characte	erized by an abnormal communication	n between the stomach and anoth	ner organ or anatomic site.	T		
Gastric hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characte	erized by bleeding from the gastric wa	all.				
Gastric necrosis	-	-	Inability to aliment adequately by GI tract; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death	
	1	I .	1	1		

Gastrointestinal disorders								
	Grade							
Adverse Event	1	2	3	4	5			
Gastric perforation Definition: A disorder characte	rized by a rupture in the stomach wa	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
			Soverely altered Cl function:	Life threatening consequences:	Death			
Gastric stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Deam			
Definition: A disorder characte	rized by a narrowing of the lumen of	the stomach.						
Gastric ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death			
	rized by a circumscribed, inflammato	T	the mucosal surface of the stomac		1			
Gastritis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated	Severely altered eating or gastric function; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characte	rized by inflammation of the stomach). !	1	I				
Gastroesophageal reflux disease	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; surgical intervention indicated	-	-			
	rized by reflux of the gastric and/or d y result in injury to the esophageal m			nd usually caused by incompetend	e of the lo			
Gastrointestinal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characte	rized by an abnormal communication	between any part of the gastroin	testinal system and another organ	or anatomic site.				
Gastrointestinal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characte	rized by a sensation of marked disco	omfort in the gastrointestinal region	1.					
Gastroparesis	Mild nausea, early satiety and bloating, able to maintain caloric intake on regular diet	Moderate symptoms; able to maintain nutrition with dietary and lifestyle modifications; may need pharmacologic intervention	Weight loss; refractory to medical intervention; unable to maintain nutrition orally	-	-			
Definition: A disorder characte	rized by an incomplete paralysis of the	he muscles of the stomach wall re	sulting in delayed emptying of the	gastric contents into the small inte	estine.			
Gingival pain	Mild pain	Moderate pain interfering with oral intake	Severe pain; inability to aliment orally	-	-			
Definition: A disorder characte	rized by a sensation of marked disco	omfort in the gingival region.	T	T				
Hemorrhoidal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characte	rized by bleeding from the hemorrho	ids.						
Hemorrhoids	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; banding or medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	-	-			
Definition: A disorder characte	rized by the presence of dilated vein	s in the rectum and surrounding a	rea.					
leal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characte	rized by an abnormal communication	between the ileum and another o	organ or anatomic site.					
leal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor	Transfusion, radiologic, endoscopic, or elective	Life-threatening consequences; urgent intervention indicated	Death			
		cauterization indicated	operative intervention indicated					

Gastrointestinal disorders						
			Grade			
Adverse Event	1	2	3	4	5	
leal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death	
Definition: A disorder characteria	zed by blockage of the normal flow	of the intestinal contents in the ile	eum.	i		
leal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death	
Definition: A disorder characteri	zed by a rupture in the ileal wall.		T	T		
leal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered Gl function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death	
Definition: A disorder characteri:	zed by a narrowing of the lumen of	the ileum.	T	T	1	
lleal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death	
Definition: A disorder characterize	zed by a circumscribed, inflammato	ory and necrotic erosive lesion on	the mucosal surface of the ileum.	Γ		
lleus	- zed by failure of the ileum to transp	Symptomatic; altered GI function; bowel rest indicated	Severely altered GI function; TPN indicated	Life-threatening consequences; urgent intervention indicated	Death	
	led by failure of the flediff to trainsp	Medical intervention or minor	Transfusion radiologic	Life-threatening consequences;	Death	
ntra-abdominal hemorrhage		cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	urgent intervention indicated	Death	
Definition: A disorder characteri:	zed by bleeding in the abdominal c	avity.	<u></u>			
Jejunal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characteri:	' zed by an abnormal communication	n between the jejunum and anoth	er organ or anatomic site.		•	
Jejunal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characteri:	zed by bleeding from the jejunal wa	all.	1	!	'	
Jejunal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death	
Definition: A disorder characteri:	zed by blockage of the normal flow	of the intestinal contents in the je	ejunum.			
Jejunal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death	
Definition: A disorder characteri:	ਾ zed by a rupture in the jejunal wall.	1	1	1	•	
Jejunal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death	
Definition: A disorder characteri	' zed by a narrowing of the lumen of	the jejunum.	·	· 	·	
lejunal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death	
Definition: A disorder characteri:	zed by a circumscribed, inflammato	ory and necrotic erosive lesion on	the mucosal surface of the jejunun	1.		
ip pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-	

Gastrointestinal disorders							
			Grade				
Adverse Event	1	2	3	4	5		
ower gastrointestinal. emorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characte	rized by bleeding from the lower gas	trointestinal tract (small intestine,	large intestine, and anus).	.			
Malabsorption	-	Altered diet; oral intervention indicated	Inability to aliment adequately; TPN indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characte	rized by inadequate absorption of nu	itrients in the small intestine. Sym	ptoms include abdominal marked o	discomfort, bloating and diarrhea.	1		
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characte	rized by inflammation of the oral mu	cosal.	1	T	1		
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-		
Definition: A disorder characte	rized by a queasy sensation and/or t	the urge to vomit.	T	Τ	1		
Obstruction gastric	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder characte	rized by blockage of the normal flow	of the contents in the stomach.		1			
Oral cavity fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characte	rized by an abnormal communication	between the oral cavity and ano	ther organ or anatomic site.				
Oral dysesthesia	Mild discomfort; not interfering with oral intake	Moderate pain; interfering with oral intake	Disabling pain; tube feeding or TPN indicated	-	-		
	rized by a burning or tingling sensati	on on the lips, tongue or entire mo	outh.	T	1		
Oral hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characte	rized by bleeding from the mouth.	,		•	•		
Oral pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-		
Definition: A disorder characte	rized by a sensation of marked disco	omfort in the mouth, tongue or lips					
Pancreatic duct stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder characte	rized by a narrowing of the lumen of	the pancreatic duct.			_		
Pancreatic fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
	rized by an abnormal communication	,	1		1		
Pancreatic hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characte	rized by bleeding from the pancreas	T	ı	ı			
Pancreatic necrosis	-	-	Tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A disorder characte	rized by a necrotic process occurring	g in the pancreas.	1	I			
Pancreatitis	-	Enzyme elevation or radiologic findings only	Severe pain; vomiting; medical intervention indicated (e.g., analgesia, nutritional support)	Life-threatening consequences; urgent intervention indicated	Death		

		Gastrointestinal dis			
			Grade		
Adverse Event	1	2	3	4	5
efinition: A disorder characte	rized by inflammation of the pancrea	S.		I	
Periodontal disease	Gingival recession or gingivitis; limited bleeding on probing; mild local bone loss	Moderate gingival recession or gingivitis; multiple sites of bleeding on probing; moderate bone loss	Spontaneous bleeding; severe bone loss with or without tooth loss; osteonecrosis of maxilla or mandible	-	-
	ngival tissue around the teeth.				
Peritoneal necrosis	-	-	Tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characte	rized by a necrotic process occurring	in the peritoneum.			
Proctitis	Rectal discomfort, intervention not indicated	Symptoms (e.g., rectal discomfort, passing blood or mucus); medical intervention indicated; limiting instrumental ADL	Severe symptoms; fecal urgency or stool incontinence; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	rized by inflammation of the rectum.				
Rectal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	rized by an abnormal communication	n between the rectum and another	r organ or anatomic site.		
Rectal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	rized by bleeding from the rectal wall	and discharged from the anus.			
Rectal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characte	rized by inflammation of the mucous	membrane of the rectum.			
Rectal necrosis	-	-	Tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characte	rized by a necrotic process occurring	in the rectal wall.		T	
Rectal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characte	rized by blockage of the normal flow	of the intestinal contents in the re		Т	
Rectal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
	rized by a sensation of marked disco	1	1_	I	L
Rectal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characte	rized by a rupture in the rectal wall.				
Rectal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characte	rized by a narrowing of the lumen of	the rectum.			
Rectal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function (e.g. altered dietary habits, vomiting, diarrhea)	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death

		Gastrointestinal dis	Older 3		
		T	Grade		
Adverse Event	1	2	3	4	5
Retroperitoneal hemorrhage	- ted by bleeding from the retroperite	Self-limited; intervention indicated	Transfusion, medical, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Salivary duct inflammation			Aguta galiyany gland nagrasis:	Life threatening concequences:	Death
Sanvary duct illianimation	Slightly thickened saliva; slightly altered taste (e.g., metallic)	markedly altered taste; alteration in diet indicated; secretion-induced symptoms; limiting instrumental ADL	Acute salivary gland necrosis; severe secretion-induced symptoms (e.g., thick saliva/oral secretions or gagging); tube feeding or TPN indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by inflammation of the salivary	duct.			
Salivary gland fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; tube feeding indicated	Severely altered GI function; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteriz	ed by an abnormal communication	n between a salivary gland and an	other organ or anatomic site.		
Small intestinal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe pain; interfering with oral intake; tube feeding, TPN or hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by inflammation of the mucous	membrane of the small intestine.			
Small intestinal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteriz	ed by blockage of the normal flow	of the intestinal contents.	_		
Small intestinal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteriz	ed by a rupture in the small intesti	ne wall.			
Small intestinal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Symptomatic and severely altered GI function; tube feeding, TPN or hospitalization indicated; non-emergent operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteriz	ed by a narrowing of the lumen of	the small intestine.			
Small intestine ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteriz	ed by a circumscribed, inflammato	ory and necrotic erosive lesion on t	the mucosal surface of the small in	testine.	
Stomach pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by a sensation of marked disco	omfort in the stomach.	1		1
Γooth development disorder	Asymptomatic; hypoplasia of tooth or enamel	Impairment correctable with oral surgery	Maldevelopment with impairment not surgically correctable; disabling	-	-
Definition: A disorder characteriz	red by a pathological process of the	e teeth occurring during tooth deve	elopment.		
Γooth discoloration	Surface stains	-	-	-	-
Definition: A disorder characteriz	ted by a change in tooth hue or tint	t.	1		
Toothache	Mild pain	Moderate pain; limiting	Severe pain; limiting self care	-	-

		Gastrointestinal dis	orders					
	Grade							
Adverse Event	1	2	3	4	5			
Typhlitis	-	-	Symptomatic (e.g., abdominal pain, fever, change in bowel habits with ileus); peritoneal signs	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characteriz	ed by inflammation of the cecum.							
Upper gastrointestinal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteriz	ed by bleeding from the upper gas	trointestinal tract (oral cavity, pha	rynx, esophagus, and stomach).					
Vomiting	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	>=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteriz	ed by the reflexive act of ejecting t	he contents of the stomach throug	gh the mouth.	•				
Gastrointestinal disorders - Other, specify	, , ,	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death			

			Grade		
Adverse Event	1	2	3	4	5
Chills	Mild sensation of cold; shivering; chattering of teeth	Moderate tremor of the entire body; narcotics indicated	Severe or prolonged, not responsive to narcotics	-	-
Definition: A disorder chara	cterized by a sensation of cold that ofte	n marks a physiologic response to	sweating after a fever.		
Death neonatal	-	-	-	-	Death
Definition: A disorder chara	cterized by cessation of life occurring du	uring the first 28 days of life.			
Death NOS	-	-	-	-	Death
Definition: A cessation of life	e that cannot be attributed to a CTCAE	term associated with Grade 5.			
Edema face	Localized facial edema	Moderate localized facial edema; limiting instrumental ADL	Severe swelling; limiting self care ADL	-	-
Definition: A disorder chara	cterized by swelling due to excessive flu	uid accumulation in facial tissues.		1	1
Edema limbs	5 - 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection	>10 - 30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL	>30% inter-limb discrepancy in volume; gross deviation from normal anatomic contour; limiting self care ADL	-	-
Definition: A disorder chara	cterized by swelling due to excessive flu	id accumulation in the upper or lo	ower extremities.		
Edema trunk	Swelling or obscuration of anatomic architecture on close inspection	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL	Gross deviation from normal anatomic contour; limiting self care ADL	-	-
Definition: A disorder chara	cterized by swelling due to excessive flu	uid accumulation in the trunk area	T	1	_
Facial pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder chara	cterized by a sensation of marked disco	omfort in the face.			
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL	-	-
Definition: A disorder chara	cterized by a state of generalized weak	ness with a pronounced inability to	summon sufficient energy to acc	omplish daily activities.	
Fever	38.0 - 39.0 degrees C (100.4 - 102.2 degrees F)	>39.0 - 40.0 degrees C (102.3 - 104.0 degrees F)	>40.0 degrees C (>104.0 degrees F) for <=24 hrs	>40.0 degrees C (>104.0 degrees F) for >24 hrs	Death
Definition: A disorder chara	cterized by elevation of the body's temp	erature above the upper limit of n	ormal.	1	
Flu like symptoms	Mild flu-like symptoms present	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder chara cough.	cterized by a group of symptoms similar	r to those observed in patients wit	h the flu. It includes fever, chills, b	ody aches, malaise, loss of appet	ite and dry
Gait disturbance	Mild change in gait (e.g., wide- based, limping or hobbling)	Moderate change in gait (e.g., wide-based, limping or hobbling); assistive device indicated; limiting instrumental ADL	Disabling; limiting self care ADL	-	-
Definition: A disorder chara	cterized by walking difficulties.	1	1	•	•
Hypothermia	-	35 - >32 degrees C; 95 - >89.6 degrees F	32 - >28 degrees C; 89.6 - >82.4 degrees F	<=28 degrees C; 82.4 degrees F; life-threatening consequences (e.g., coma, hypotension, pulmonary edema, acidemia, ventricular fibrillation)	1

Grade						
Adverse Event	1	2	3	4	5	
nfusion related reaction	Mild transient reaction; infusion	Therapy or infusion interruption	Prolonged (e.g., not rapidly	Life-threatening consequences;	Death	
illiusion relateu reaction	interruption not indicated;	indicated but responds promptly	responsive to symptomatic	urgent intervention indicated	Death	
	intervention not indicated	to symptomatic treatment (e.g.,	medication and/or brief	argoni intervention indicated		
	intervention net maietate	antihistamines, NSAIDS,	interruption of infusion);			
		narcotics, IV fluids); prophylactic				
		medications indicated for <=24	following initial improvement;			
		hrs	hospitalization indicated for			
			clinical sequelae			
Definition: A disorder characteriz	। zed by adverse reaction to the infus	ı sion of pharmacological or biologic		I	1	
nfusion site extravasation	,	Erythema with associated	Ulceration or necrosis; severe	Life-threatening consequences;	Death	
The same that are same to the		symptoms (e.g., edema, pain,	tissue damage; operative	urgent intervention indicated	Dou	
		induration, phlebitis)	intervention indicated	angent intervention introduce		
Definition: A disorder characteria	। zed by leakage of a pharmacologic	, , , ,	1	I sella. Signs and symptoms include	l e induratio	
	sation and marked discomfort at the	•	musion site into the surrounding to	sauc. Oigna and symptoma moldus	o induratio	
njection site reaction	Tenderness with or without	Pain; lipodystrophy; edema;	Ulceration or necrosis; severe	Life-threatening consequences;	Death	
•	associated symptoms (e.g.,	phlebitis	tissue damage; operative	urgent intervention indicated		
	warmth, erythema, itching)	•	intervention indicated			
Definition: A disorder characteriz	zed by an intense adverse reaction	ı (usually immunologic) developing	1	I	1	
rritability	Mild; easily consolable	Moderate; limiting instrumental	Severe abnormal or excessive	_	_	
iritability	Wind, Cabily Corrobiable	ADL; increased attention	response; limiting self care ADL;			
		indicated	inconsolable			
5 5 W A II A II A I		Į.	1	l	1	
Definition: A disorder characterize	zed by an abnormal responsivenes	s to stimuli or physiological arousa	ar; may be in response to pain, ing	nt, a drug, an emotional situation (or a medic	
_ocalized edema	Localized to dependent areas,	Moderate localized edema and	Severe localized edema and	-	_	
	no disability or functional	intervention indicated; limiting	intervention indicated; limiting			
	impairment	instrumental ADL	self care ADL			
Definition: Δ disorder characteria	ed by swelling due to excessive flu	ı	1	ı	ı	
Malaise	Uneasiness or lack of well being	·	omic sitc.			
vialaise	Office strices of fack of well being	being; limiting instrumental ADL	-	-	-	
			1	l	I	
Definition: A disorder characteria	red by a feeling of general discomf	art or unesciness an out-of-sorts				
	red by a feeling of general discomfo	ort or uneasiness, an out-of-sorts		Life threatening concessioned	Dooth	
	red by a feeling of general discomfe	ort or uneasiness, an out-of-sorts	Shock with azotemia and acid-	Life-threatening consequences	Death	
	ted by a feeling of general discomform	ort or uneasiness, an out-of-sorts	Shock with azotemia and acid- base disturbances; significant	(e.g., vasopressor dependent	Death	
	ted by a feeling of general discomfo	ort or uneasiness, an out-of-sorts	Shock with azotemia and acid-	(e.g., vasopressor dependent and oliguric or anuric or	Death	
	ted by a feeling of general discomfo	ort or uneasiness, an out-of-sorts	Shock with azotemia and acid- base disturbances; significant	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic	Death	
Multi-organ failure	-	-	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities	(e.g., vasopressor dependent and oliguric or anuric or	Death	
Multi-organ failure Definition: A disorder characteriz	eed by progressive deterioration of	the lungs, liver, kidney and clottin	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic	Death	
Multi-organ failure	eed by progressive deterioration of Asymptomatic localized neck	the lungs, liver, kidney and clottin Moderate neck edema; slight	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities g mechanisms.	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic	Death	
Multi-organ failure Definition: A disorder characteriz	eed by progressive deterioration of	- the lungs, liver, kidney and clottin Moderate neck edema; slight obliteration of anatomic	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities g mechanisms. Generalized neck edema (e.g., difficulty in turning neck);	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic	Death	
Multi-organ failure Definition: A disorder characteriz	eed by progressive deterioration of Asymptomatic localized neck	the lungs, liver, kidney and clottin Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities g mechanisms.	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic	Death	
Multi-organ failure Definition: A disorder characteriz Neck edema	eed by progressive deterioration of Asymptomatic localized neck edema	the lungs, liver, kidney and clottin Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities g mechanisms. Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic	Death -	
Multi-organ failure Definition: A disorder characteriz Neck edema Definition: A disorder characteriz	ced by progressive deterioration of Asymptomatic localized neck edema	the lungs, liver, kidney and clotting Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL tition of excessive fluid in the neck	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities g mechanisms. Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic	Death -	
Multi-organ failure Definition: A disorder characteriz Neck edema Definition: A disorder characteriz	eed by progressive deterioration of Asymptomatic localized neck edema	the lungs, liver, kidney and clotting Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL tition of excessive fluid in the neck	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities g mechanisms. Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL Severe pain; limiting self care	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic	Death -	
Multi-organ failure Definition: A disorder characteriz Neck edema Definition: A disorder characteriz Non-cardiac chest pain	ced by progressive deterioration of Asymptomatic localized neck edema ed by swelling due to an accumula	the lungs, liver, kidney and clotting Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL tion of excessive fluid in the neck Moderate pain; limiting instrumental ADL	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities g mechanisms. Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic	Death -	
Multi-organ failure Definition: A disorder characteriz Neck edema Definition: A disorder characteriz Non-cardiac chest pain Definition: A disorder characteriz	ced by progressive deterioration of Asymptomatic localized neck edema ted by swelling due to an accumula Mild pain	the lungs, liver, kidney and clotting Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL tition of excessive fluid in the neck Moderate pain; limiting instrumental ADL ated to a heart disorder.	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities g mechanisms. Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL Severe pain; limiting self care ADL	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic	Death -	
Multi-organ failure Definition: A disorder characteriz Neck edema Definition: A disorder characteriz Non-cardiac chest pain Definition: A disorder characteriz	ced by progressive deterioration of Asymptomatic localized neck edema ed by swelling due to an accumula	the lungs, liver, kidney and clotting Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL tition of excessive fluid in the neck Moderate pain; limiting instrumental ADL ated to a heart disorder. Moderate pain; limiting	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities g mechanisms. Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL Severe pain; limiting self care ADL	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic	Death -	
Multi-organ failure Definition: A disorder characteriz Neck edema Definition: A disorder characteriz Non-cardiac chest pain Definition: A disorder characteriz Pain	eed by progressive deterioration of Asymptomatic localized neck edema ted by swelling due to an accumulated by discomfort in the chest unrelement of the pain tends of the chest unrelement of the ch	the lungs, liver, kidney and clottin Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL tion of excessive fluid in the neck Moderate pain; limiting instrumental ADL ated to a heart disorder. Moderate pain; limiting instrumental ADL	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities g mechanisms. Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL Severe pain; limiting self care ADL	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic	Death -	
Multi-organ failure Definition: A disorder characteriz Neck edema Definition: A disorder characteriz Non-cardiac chest pain Definition: A disorder characteriz Pain Definition: A disorder characteriz	ced by progressive deterioration of Asymptomatic localized neck edema ted by swelling due to an accumula Mild pain	the lungs, liver, kidney and clottin Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL tion of excessive fluid in the neck Moderate pain; limiting instrumental ADL ated to a heart disorder. Moderate pain; limiting instrumental ADL	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities g mechanisms. Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL Severe pain; limiting self care ADL	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic acidosis)	-	
Multi-organ failure Definition: A disorder characteriz Neck edema Definition: A disorder characteriz Non-cardiac chest pain Definition: A disorder characteriz Pain Definition: A disorder characteriz Sudden death NOS	eed by progressive deterioration of Asymptomatic localized neck edema eed by swelling due to an accumulated by discomfort in the chest unreleased by the sensation of marked discomfort in the discomfort in the chest unreleased by the sensation of marked discomfort in the chest unreleased by the sensation of the chest unreleased by the chest unreleased by the chest unrel	the lungs, liver, kidney and clotting Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL tition of excessive fluid in the neck Moderate pain; limiting instrumental ADL ated to a heart disorder. Moderate pain; limiting instrumental ADL comfort, distress or agony.	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities g mechanisms. Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL Severe pain; limiting self care ADL Severe pain; limiting self care	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic	Death Death	
Multi-organ failure Definition: A disorder characteriz Neck edema Definition: A disorder characteriz Non-cardiac chest pain Definition: A disorder characteriz Pain Definition: A disorder characteriz Sudden death NOS Definition: An unexpected cessa	eed by progressive deterioration of Asymptomatic localized neck edema eed by swelling due to an accumulated by discomfort in the chest unreleful pain eed by the sensation of marked discussion of life that cannot be attributed	the lungs, liver, kidney and clotting Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL tion of excessive fluid in the neck Moderate pain; limiting instrumental ADL lated to a heart disorder. Moderate pain; limiting instrumental ADL comfort, distress or agony. - to a CTCAE term associated with	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities g mechanisms. Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL Severe pain; limiting self care ADL Severe pain; limiting self care ADL	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic acidosis) -	Death	
Multi-organ failure Definition: A disorder characteriz Neck edema Definition: A disorder characteriz Non-cardiac chest pain Definition: A disorder characteriz Pain Definition: A disorder characteriz Sudden death NOS Definition: An unexpected cessa General disorders and	eed by progressive deterioration of Asymptomatic localized neck edema eed by swelling due to an accumula Mild pain eed by discomfort in the chest unrel Mild pain eed by the sensation of marked disc toon of life that cannot be attributed Asymptomatic or mild	the lungs, liver, kidney and clotting Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL stion of excessive fluid in the neck Moderate pain; limiting instrumental ADL ated to a heart disorder. Moderate pain; limiting instrumental ADL comfort, distress or agony. - to a CTCAE term associated with	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities g mechanisms. Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL Severe pain; limiting self care ADL Severe pain; limiting self care ADL - n Grade 5. Severe or medically significant	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic acidosis) - - Life-threatening consequences;	-	
Multi-organ failure Definition: A disorder characteriz Neck edema Definition: A disorder characteriz Non-cardiac chest pain Definition: A disorder characteriz Pain Definition: A disorder characteriz Sudden death NOS Definition: An unexpected cessa General disorders and administration site conditions -	ted by progressive deterioration of Asymptomatic localized neck edema and by swelling due to an accumulated by discomfort in the chest unreleading by the sensation of marked discomplete of the complete of	the lungs, liver, kidney and clottine Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL tition of excessive fluid in the neck Moderate pain; limiting instrumental ADL ated to a heart disorder. Moderate pain; limiting instrumental ADL comfort, distress or agony. - to a CTCAE term associated with Moderate; minimal, local or noninvasive intervention	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities g mechanisms. Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL Severe pain; limiting self care ADL Severe pain; limiting self care ADL - a Grade 5. Severe or medically significant but not immediately life-	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic acidosis) -	Death	
Multi-organ failure Definition: A disorder characteriz Neck edema Definition: A disorder characteriz Non-cardiac chest pain Definition: A disorder characteriz Pain Definition: A disorder characteriz Sudden death NOS Definition: An unexpected cessa	eed by progressive deterioration of Asymptomatic localized neck edema eed by swelling due to an accumulated by discomfort in the chest unreceded by the sensation of marked discertain of life that cannot be attributed asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention	the lungs, liver, kidney and clottine Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL tition of excessive fluid in the neck Moderate pain; limiting instrumental ADL atted to a heart disorder. Moderate pain; limiting instrumental ADL comfort, distress or agony. - to a CTCAE term associated with Moderate; minimal, local or noninvasive intervention indicated; limiting age-	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities g mechanisms. Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL Severe pain; limiting self care ADL Severe pain; limiting self care ADL - n Grade 5. Severe or medically significant but not immediately life- threatening; hospitalization or	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic acidosis) - - Life-threatening consequences;	Death	
Multi-organ failure Definition: A disorder characteriz Neck edema Definition: A disorder characteriz Non-cardiac chest pain Definition: A disorder characteriz Pain Definition: A disorder characteriz Sudden death NOS Definition: An unexpected cessa General disorders and administration site conditions -	ted by progressive deterioration of Asymptomatic localized neck edema and by swelling due to an accumulated by discomfort in the chest unreleading by the sensation of marked discomplete of the complete of	the lungs, liver, kidney and clottine Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL tition of excessive fluid in the neck Moderate pain; limiting instrumental ADL ated to a heart disorder. Moderate pain; limiting instrumental ADL comfort, distress or agony. - to a CTCAE term associated with Moderate; minimal, local or noninvasive intervention	Shock with azotemia and acid- base disturbances; significant coagulation abnormalities g mechanisms. Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL Severe pain; limiting self care ADL Severe pain; limiting self care ADL - a Grade 5. Severe or medically significant but not immediately life-	(e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic acidosis) - - Life-threatening consequences;	Death	

		Hepatobiliary diso	rders		
			Grade		
Adverse Event	1	2	3	4	5
Bile duct stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; IV fluids indicated <24 hrs	Severely altered GI function; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteriz	red by a narrowing of the lumen of	the bile duct.		1	
Biliary fistula	-	Symptomatic and intervention not indicated	Severely altered GI function; TPN indicated; endoscopic intervention indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteriz	red by an abnormal communication	n between the bile ducts and anoth	ner organ or anatomic site.	I	
Cholecystitis	-	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteriz	red by inflammation involving the g	allbladder. It may be associated w	vith the presence of gallstones.		
Gallbladder fistula	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Symptomatic or severely altered GI function; TPN indicated; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteriz	red by an abnormal communication	between the gallbladder and and	ther organ or anatomic site.		
Gallbladder necrosis	-	-	-	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characterization	red by a necrotic process occurring	g in the gallbladder.	T	Г	
Gallbladder obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; IV fluids indicated <24 hrs	Symptomatic and severely altered GI function; tube feeding, TPN or hospitalization indicated; non-emergent operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
	red by blockage of the normal flow				
Gallbladder pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	red by a sensation of marked disco	omfort in the gallbladder region.			•
Gallbladder perforation	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	red by a rupture in the gallbladder	-	Asterixis; mild encephalopathy; limiting self care ADL	Moderate to severe encephalopathy; coma; life-threatening consequences	Death
	red by the inability of the liver to m	etabolize chemicals in the body. L	aboratory test results reveal abnor	mal plasma levels of ammonia, bi	lirubin, lac
dehydrogenase, and alkaline ph		I -		T .	
Hepatic hemorrhage	Mild; intervention not indicated	Symptomatic; medical intervention indicated	Transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by bleeding from the liver.				
Hepatic necrosis	-	-	-	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characteriz	red by a necrotic process occurring	in the hepatic parenchyma.		.	
Hepatic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by a sensation of marked disco	omfort in the liver region.			
Perforation bile duct	-	-	Radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention	Death

		Hepatobiliary diso	rders				
Grade							
Adverse Event	1	2	3	4	5		
Portal hypertension	-	Decreased portal vein flow	Reversal/retrograde portal vein flow; associated with varices and/or ascites	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characterize	ed by an increase in blood pressu	re in the portal venous system.					
Portal vein thrombosis	-	Intervention not indicated	Medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characterize	ed by the formation of a thrombus	(blood clot) in the portal vein.					
Hepatobiliary disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated;	Life-threatening consequences; urgent intervention indicated	Death		
			disabling; limiting self care ADL				

		Immune system dis	orders		
			Grade		
Adverse Event	1	2	3	4	5
Allergic reaction	Transient flushing or rash, drug fever <38 degrees C (<100.4 degrees F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
	zed by an adverse local or general	response from exposure to an alle			I
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
	zed by an acute inflammatory react resents with breathing difficulty, di				ypersensitivi
Autoimmune disorder					Dooth
Autoimmune disorder	Asymptomatic; serologic or other evidence of autoimmune reaction, with normal organ function; intervention not indicated	Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism)	Autoimmune reactions involving major organ (e.g., colitis, anemia, myocarditis, kidney)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder resulting fr	om loss of function or tissue destru	iction of an organ or multiple orga	ns, arising from humoral or cellula	r immune responses of the individe	ual to his ow
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilatory support indicated	Death
Definition: A disorder characterize	red by nausea, headache, tachyca	rdia, hypotension, rash, and shorti	ness of breath; it is caused by the	release of cytokines from the cells	i.
Serum sickness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate arthralgia; fever, rash, urticaria, antihistamines indicated	Severe arthralgia or arthritis; extensive rash; steroids or IV fluids indicated	Life-threatening consequences; pressor or ventilatory support indicated	Death
	red by a delayed-type hypersensiti e foreign antigen. Symptoms inclu				
Immune system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

		Infections and infes	tations		
			Grade		
Adverse Event	1	2	3	4	5
Abdominal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	rized by an infectious process invol	ving the abdominal cavity.		T	
Anorectal infection	Localized; local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	rized by an infectious process invol	ving the anal area and the rectum.	IV antibiotic antifungal or	Life threatening consequences:	Death
Appendicitis			IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Deam
	rized by acute inflammation to the		1		ъ "
Appendicitis perforated	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	rized by acute inflammation to the viceal wall rupture causes the releas	vermiform appendix caused by a pa	athogenic agent with gangrenous o	changes resulting in the rupture of	the
Arteritis infective	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	rized by an infectious process invol	ving an artery.			
Biliary tract infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	rized by an infectious process invol	ving the biliary tract.	1	ı	ı
Bladder infection	-	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	rized by an infectious process invol	ving the bladder.			
Bone infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	rized by an infectious process invol		T		
Breast infection	-	Local infection with moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	Severe infection; axillary adenitis; IV antibacterial, antifungal, or antiviral intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	rized by an infectious process invol	1			
Bronchial infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	rized by an infectious process invol	1		1	
Catheter related infection	-	Localized; local intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	rized by an infectious process that	arises secondary to catheter use.			
Cecal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

		Infections and infes	Grade		
Adverse Event	1	2	3	4	5
	ed by an infectious process involv		, and the second	7	
Cervicitis infection	ed by an intections process involv	Localized; local intervention	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
Cervicius irriection		indicated (e.g., topical antibiotic,	antiviral intervention indicated;	urgent intervention indicated	Death
		antifungal, or antiviral)	radiologic or operative	g	
			intervention indicated		
Definition: A disorder characterize	ed by an infectious process involv	ing the uterine cervix.			
Conjunctivitis infective	-	Localized; local intervention	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
		indicated (e.g., topical antibiotic,	antiviral intervention indicated;	urgent intervention indicated	
		antifungal, or antiviral)	radiologic or operative		
			intervention indicated	1	l
	ed by an infectious process involv		· ·		1
Corneal infection	-	Localized; local intervention	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
		indicated (e.g., topical antibiotic, antifungal, or antiviral)	antiviral intervention indicated; radiologic or operative	urgent intervention indicated	
		a	intervention indicated		
Definition: A disorder characterize	। ed by an infectious process involv	ing the cornea.	1	1	1
Cranial nerve infection	-	-	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
			antiviral intervention indicated;	urgent intervention indicated	
			radiologic or operative		
			intervention indicated		
Definition: A disorder characterize	ed by an infectious process involv	ing a cranial nerve.	_		ı
Device related infection	-	-	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
			antiviral intervention indicated;	urgent intervention indicated	
			radiologic or operative		
			intervention indicated	1	l
	ed by an infectious process involv	I	T	I	I
Duodenal infection	-	Moderate symptoms; medical	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
		intervention indicated (e.g., oral antibiotics)	antiviral intervention indicated; radiologic or operative	urgent intervention indicated	
			intervention indicated		
Definition: A disorder characterize	ed by an infectious process involv	ing the duodenum.	'	•	•
Encephalitis infection	-	-	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
			antiviral intervention indicated;	urgent intervention indicated	
			severe changes in mental		
			status; self-limited seizure		
			activity; focal neurologic		
5 6 W A P 1 1 4 4 5			abnormalities		
	ed by an infectious process involv	ing the brain tissue.	ny erie er		l
Encephalomyelitis infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated;	Life-threatening consequences; urgent intervention indicated	Death
			radiologic or operative	argoni intervention indicated	
			intervention indicated		
Definition: A disorder characterize	ed by an infectious process involv	ing the brain and spinal cord tissu	es.	•	•
Endocarditis infective		-	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
			antiviral intervention indicated;	urgent intervention indicated	
			radiologic or operative		
			intervention indicated		
3 C 10 A 10 I I I I I	ed by an infectious process involv	ing the endocardial layer of the he	art.		
Definition: A disorder characterize					
Definition: A disorder characterize	-	Local intervention indicated	Systemic intervention or	Blindness (20/200 or worse)	-

		Grade					
Adverse Event	1	2	3	4	5		
Enterocolitis infectious	•	Passage of >3 unformed stools	IV antibiotic, antifungal, or	Life-threatening consequences;	Death		
Enterocontis infectious	-	per 24 hrs or duration of illness	antiviral intervention indicated;	urgent intervention indicated	Dealli		
		l'	· ·	digent intervention indicated			
		>48 hrs; moderate abdominal	radiologic, endoscopic, or				
		pain	operative intervention indicated;				
			profuse watery diarrhea with				
			signs of hypovolemia; bloody				
			diarrhea; fever; severe				
			abdominal pain; hospitalization				
			indicated				
Definition: A disorder characteriz	red by an infectious process involv	ing the small and large intestines.	ı	ı	1		
sophageal infection	T ₋	Local intervention indicated	IV antibiotic, antifungal, or	Life-threatening consequences;	Death		
.sepriagear iniceneri		(e.g., oral antibiotic, antifungal,	antiviral intervention indicated;	urgent intervention indicated	2000		
				argent intervention indicated			
		antiviral)	radiologic or operative				
	1		intervention indicated	l			
efinition: A disorder characteriz	red by an infectious process involv	ing the esophagus.	T	T			
Eye infection	-	Localized; local intervention	IV antibiotic, antifungal, or	Life-threatening consequences;	Death		
		indicated (e.g., topical antibiotic,	antiviral intervention indicated;	urgent intervention indicated;			
		antifungal, or antiviral)	radiologic or operative	enucleation			
		,	intervention indicated				
Definition: A disorder characterize	। ed by an infectious process involv	ing the eve	1	ı	1		
Gallbladder infection	Sa Sy an iniconous process involv	ing the eye.	IV antibiotic antifunction	Life threatening con	Dogu		
Galibladder infection	1-	-	IV antibiotic, antifungal, or	Life-threatening consequences;	Death		
			antiviral intervention indicated;	urgent intervention indicated			
			radiologic, endoscopic, or				
			operative intervention indicated				
Definition: A disorder characteriz	ed by an infectious process involv	ing the gallbladder.					
Gum infection	Local therapy indicated (swish	Moderate symptoms; oral	IV antibiotic, antifungal, or	Life-threatening consequences;	Death		
	and swallow)	intervention indicated (e.g.,	antiviral intervention indicated;	urgent intervention indicated			
	'	antibiotic, antifungal, antiviral)	radiologic or operative	"			
		a	intervention indicated				
Definition: A disorder characteris	l ed by an infectious process involv	ing the gums	1	I	ı		
	led by all illiections process litvolv	ing the guins.	N/		D41-		
Hepatic infection	-	-	IV antibiotic, antifungal, or	Life-threatening consequences;	Death		
			antiviral intervention indicated;	urgent intervention indicated			
			radiologic or operative				
			intervention indicated				
Definition: A disorder characteriz	ed by an infectious process involv	ing the liver.	1	I			
Hepatitis viral	Asymptomatic, treatment not	-	Symptomatic liver dysfunction;	Decompensated liver function	Death		
	indicated		fibrosis by biopsy; compensated	(e.g., ascites, coagulopathy,			
			cirrhosis; reactivation of chronic	encephalopathy, coma)			
			hepatitis	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,			
Definition: A disorder characteriz	। ed by a viral pathologic process in	volving the liver parenchyma	1 .	!	1		
		1	IV antibiotic antifuncel or	Life threatening consequences:	Death		
Infective myositis	1-	Localized; local intervention	IV antibiotic, antifungal, or	Life-threatening consequences;	Death		
		indicated (e.g., topical antibiotic,	antiviral intervention indicated;	urgent intervention indicated			
		antifungal, or antiviral)	radiologic or operative				
			intervention indicated				
Definition: A disorder characteriz	ed by an infectious process involv	ing the skeletal muscles.	T				
Joint infection	-	Localized; local intervention	Arthroscopic intervention	Life-threatening consequences;	Death		
		indicated; oral intervention	indicated (e.g., drainage) or	urgent intervention indicated			
		indicated (e.g., antibiotic,	arthrotomy (e.g., open surgical				
		antifungal, antiviral); needle	drainage)				
		aspiration indicated (single or	"				
		multiple)					
Definition: A disorder characterize	। ed by an infectious process involv	1	1	I	1		
	.ou by an inicollous process involv	ing a joint.	N/ antibiatio	Life threatering	D"		
Kidney infection	-	-	IV antibiotic, antifungal, or	Life-threatening consequences;	Death		
			antiviral intervention indicated;	urgent intervention indicated			
			radiologic, endoscopic, or				
			radiologic, endoscopic, or operative intervention indicated				

Infections and infestations								
			Grade					
Adverse Event	1	2	3	4	5			
_aryngitis	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder charac	cterized by an inflammatory process i	nvolving the larynx.	1					
Lip infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	-	-			
Definition: A disorder charac	cterized by an infectious process invo	lving the lips.						
Lung infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder charac	cterized by an infectious process invo	lving the lungs.						
Lymph gland infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder charac	cterized by an infectious process invo	lving the lymph nodes.	T	1				
Mediastinal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder charac	cterized by an infectious process invo	lving the mediastinum.	,					
Meningitis	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated; focal neurologic deficit	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder charac	cterized by acute inflammation of the	meninges of the brain and/or spinal	cord.	•	•			
Mucosal infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder charac	cterized by an infectious process invo	lving a mucosal surface.	T	1	1			
Nail infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	-	-			
Definition: A disorder charac	cterized by an infectious process invo	lving the nail.						
Otitis externa	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
	cterized by an infectious process invo ymptoms include fullness, itching, swe	-	•	ive water exposure (swimmer's ea	r infection			
Otitis media	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder charac	terized by an infectious process invo	lving the middle ear.	1	'	'			
Ovarian infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative	Life-threatening consequences; urgent intervention indicated	Death			

		Infections and infes	tations		
			Grade		
Adverse Event	1	2	3	4	5
Pancreas infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	erized by an infectious process involv	ing the pancreas.			
Papulopustular rash	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; lifethreatening consequences	Death
	erized by an eruption consisting of pa				o, and upper
	this rash does not present with whiteh		i i	esions.	
Paronychia	Nail fold edema or erythema; disruption of the cuticle	Localized intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	Surgical intervention or IV antibiotics indicated; limiting self care ADL	-	-
Definition: A disorder characte	erized by an infectious process involvi	ing the soft tissues around the nai	l		
Pelvic infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder character	erized by an infectious process involving	ing the pelvic cavity.	1	<u> </u>	
Penile infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	erized by an infectious process involvi	ing the penis.			
Periorbital infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	erized by an infectious process involvi		N/	if_	D41-
Peripheral nerve infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	erized by an infectious process involvi	ing the peripheral nerves.		l .	
Peritoneal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder character	erized by an infectious process involvi	ing the peritoneum.	1		
Pharyngitis	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder character	erized by inflammation of the throat.	· 			
Phlebitis infective	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

Infections and infestations							
			Grade				
Adverse Event	1	2	3	4	5		
Definition: A disorder characterize of the infected vein.	ed by an infectious process involvi	ng the vein. Clinical manifestation	s include erythema, marked disco	omfort, swelling, and induration alo	ng the course		
Pleural infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characterize	ed by an infectious process involvi	ng the pleura.					
Prostate infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characterize	ed by an infectious process involvi	ng the prostate gland.	T	1			
Rash pustular	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	-	-		
Definition: A disorder characterize	ed by a circumscribed and elevate	d skin lesion filled with pus.	T	1			
Rhinitis infective	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	-	-	-		
	ed by an infectious process involvi	ng the nasal mucosal.	T	T	1		
Salivary gland infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characterize	ed by an infectious process involvi	ng the salivary gland.	T	_			
Scrotal infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
	ed by an infectious process involvi I	ng the scrotum.	<u> </u>				
Sepsis	-	-	-	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characterize	ed by the presence of pathogenic	microorganisms in the blood strea	m that cause a rapidly progressing	g systemic reaction that may lead	to shock.		
Sinusitis	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characterize	ed by an infectious process involvi	ng the mucous membranes of the	paranasal sinuses.				
Skin infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
	ed by an infectious process involvi		I	1			
Small intestine infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
	ed by an infectious process involvi I		<u> </u>	<u> </u>			
Soft tissue infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characterize	ed by an infectious process involvi	ng soft tissues.	Т	Т			
Splenic infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		

Infections and infestations Grade							
			Grade		_		
Adverse Event	1	2	3	4	5		
Definition: A disorder characteri Stoma site infection	zed by an infectious process involv Localized, local intervention indicated	ing the spleen. Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteri	zed by an infectious process involv	ing a stoma (surgically created op	ening on the surface of the body).	'	•		
Tooth infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteri	zed by an infectious process involv	ing a tooth.	T				
Tracheitis		Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
	zed by an infectious process involv	T	N/ antibiatio antifungal as	Life threatening concessions	Dooth		
Upper respiratory infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteri	zed by an infectious process involv	ing the upper respiratory tract (nos	se, paranasal sinuses, pharynx, la	rynx, or trachea).	т		
Urethral infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteri	zed by an infectious process involv	ing the urethra.					
Urinary tract infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteri	zed by an infectious process involv	ing the urinary tract, most commo	nly the bladder and the urethra.	'	•		
Uterine infection		Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteri	zed by an infectious process involv	ing the endometrium. It may exten	d to the myometrium and parame	trial tissues.			
Vaginal infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteri	zed by an infectious process involv	ing the vagina.	T	T			
Vulval infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteri	zed by an infectious process involv	ing the vulva.					
Wound infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteri	zed by an infectious process involv	ing the wound.	1	1			
Infections and infestations - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death		

Grade							
Adverse Event	1	2	3	4	5		
Ankle fracture	Mild; non-surgical intervention	Limiting instrumental ADL;	Limiting self care ADL; elective	-			
	indicated	operative intervention indicated	surgery indicated				
Definition: A finding of damage in	to the ankle joint characterized by a	a break in the continuity of the ank	ie bone. Symptoms include marke	a discomfort, swelling and diπicult	y moving th		
Aortic injury	I_	_	Severe symptoms; limiting self	Life-threatening consequences;	Death		
			care ADL; disabling; repair or	evidence of end organ damage;			
			revision indicated	urgent operative intervention			
				indicated	l		
Definition: A finding of damage		<u> </u>	Ī		I		
Arterial injury	Asymptomatic diagnostic	Symptomatic (e.g.,	Severe symptoms; limiting self	Life-threatening consequences;	Death		
	finding; intervention not indicated	claudication); repair or revision not indicated	care ADL; disabling; repair or revision indicated	evidence of end organ damage; urgent operative intervention			
	in a sate a	The maistrea		indicated			
Definition: A finding of damage	to an artery.						
Biliary anastomotic leak	Asymptomatic diagnostic	Symptomatic; medical	Severe symptoms; radiologic,	Life-threatening consequences;	Death		
	observations only; intervention	intervention indicated	endoscopic or elective operative	urgent operative intervention			
	not indicated		intervention indicated	indicated	1		
Definition: A finding of leakage	of bile due to breakdown of a biliary	anastomosis (surgical connection	n of two separate anatomic structul	res). I	Т		
Bladder anastomotic leak	Asymptomatic diagnostic	Symptomatic; medical	Severe symptoms; radiologic,	Life-threatening consequences;	Death		
	observations only; intervention not indicated	intervention indicated	endoscopic or elective operative intervention indicated	urgent operative intervention indicated			
Definition: A finding of leakage	of urine due to breakdown of a blad	l der anastomosis (surgical connec	1	•	I		
Bruising	Localized or in a dependent	Generalized	-	_	Ι_		
nuising	area	Generalized					
Definition: A finding of injury of t	the soft tissues or bone characterize	ed by leakage of blood into surrou	nding tissues.	'	•		
Burn	Minimal symptoms; intervention	Medical intervention; minimal	Moderate to major debridement	Life-threatening consequences	Death		
	not indicated	debridement indicated	or reconstruction indicated				
Definition: A finding of impaired	integrity to the anatomic site of an	adverse thermal reaction. Burns c	an be caused by exposure to cher	nicals, direct heat, electricity, flam	es and		
adiation. The extent of damage	e depends on the length and intensi	ty of exposure and time until provi	sion of treatment.				
Dermatitis radiation	Faint erythema or dry	Moderate to brisk erythema;	Moist desquamation in areas	Life-threatening consequences;	Death		
	desquamation	patchy moist desquamation, mostly confined to skin folds	other than skin folds and creases; bleeding induced by	skin necrosis or ulceration of full thickness dermis; spontaneous			
		and creases; moderate edema	minor trauma or abrasion	bleeding from involved site; skin			
				graft indicated			
Definition: A finding of cutaneou	is inflammatory reaction occurring a	as a result of exposure to biologica	ally effective levels of ionizing radia	ation.			
Esophageal anastomotic leak	Asymptomatic diagnostic	Symptomatic; medical	Severe symptoms; radiologic,	Life-threatening consequences;	Death		
	observations only; intervention	intervention indicated	endoscopic or elective operative	urgent operative intervention			
	not indicated		intervention indicated	indicated	I		
	due to breakdown of an esophagea			res).			
Fall	Minor with no resultant injuries; intervention not indicated	Symptomatic; noninvasive intervention indicated	Hospitalization indicated	-	-		
Definition: A finding of sudden r	novement downward, usually result	1	I		I		
Fallopian tube anastomotic leak		Symptomatic; medical	Severe symptoms; radiologic,	Life-threatening consequences;	Death		
-allopian tube anastomotic leak	diagnostic observations only;	intervention indicated	endoscopic or elective operative	I	Death		
	intervention not indicated		intervention indicated	indicated			
Definition: A finding of leakage	due to breakdown of a fallopian tub	e anastomosis (surgical connection	n of two separate anatomic structu	ıres).			
Fallopian tube perforation	Asymptomatic diagnostic	Symptomatic and intervention	Severe symptoms; elective	Life-threatening consequences;	Death		
	observations only; intervention	not indicated	operative intervention indicated	urgent operative intervention			
	not indicated			indicated (e.g., organ resection)	I		
Definition: A finding of rupture o		1	1		1		
racture	Asymptomatic; clinical or	Symptomatic but non-displaced;		Life-threatening consequences;	Death		
	diagnostic observations only;	immobilization indicated	open wound with bone	urgent intervention indicated			
	intervention not indicated		exposure; disabling; operative intervention indicated				
	ा injury to the bone in which the con	1	1	Į.	1		

Grade								
Adverse Event	1	2	3	4	5			
Gastric anastomotic leak	Asymptomatic diagnostic	Symptomatic; medical	Severe symptoms; radiologic,	Life-threatening consequences;	Death			
	observations only; intervention	intervention indicated	endoscopic or elective operative	urgent operative intervention				
	not indicated		intervention indicated	indicated				
Definition: A finding of leakage d	ue to breakdown of a gastric anas	tomosis (surgical connection of tw	o separate anatomic structures).	•				
Gastrointestinal anastomotic	Asymptomatic diagnostic	Symptomatic; medical	Severe symptoms; radiologic,	Life-threatening consequences;	Death			
leak	observations only; intervention	intervention indicated	endoscopic or elective operative	urgent operative intervention	Journ			
	not indicated		intervention indicated	indicated				
Definition: A finding of leakage d	। ue to breakdown of a gastrointesti	ı nal anastomosis (surgical connect	ion of two separate anatomic struc	tures).	1			
Gastrointestinal stoma necrosis	1.	Superficial necrosis;	Severe symptoms;	Life-threatening consequences;	Death			
Custion Resultar Storia Necrosis		intervention not indicated	hospitalization or elective	urgent intervention indicated	Bouiii			
		intervention net indicated	operative intervention indicated	argent intervention indicated				
Definition: A finding of a necrotic	process occurring in the gastroint	l estinal tract stoma	1 '	l	ļ			
	process occurring in the gastroine		Cavera nain, beanitalization or	Life threatening concessions				
Hip fracture	-	Hairline fracture; mild pain;	Severe pain; hospitalization or	Life-threatening consequences;	-			
		limiting instrumental ADL; non- surgical intervention indicated	intervention indicated for pain control (e.g., traction); operative	symptoms associated with neurovascular compromise				
		Jangioai intervention indicated	intervention indicated	mourovasoulai compromise				
Definition: A finding of troumatic	injury to the hip in which the continu	l nuity of either the femoral bood fo	1	htrochanteric regions is broken	I			
	injury to the hip in which the contir	idity of either the femoral nead, fe			L			
Injury to carotid artery	-	-	Severe symptoms; limiting self	Life-threatening consequences;	Death			
			care ADL (e.g., transient	urgent intervention indicated				
			cerebral ischemia); repair or revision indicated					
D-5-141 A 5 4 4-	 		revision indicated		l			
Definition: A finding of damage to	the carolid artery.		1		I			
Injury to inferior vena cava	-	-	-	Life-threatening consequences;	Death			
	1			urgent intervention indicated	I			
Definition: A finding of damage to	the inferior vena cava.							
Injury to jugular vein	-	-	Symptomatic limiting self care	Life-threatening consequences;	Death			
			ADL; disabling; repair or	urgent intervention indicated				
			revision indicated					
			•	•	•			
Definition: A finding of damage to	the jugular vein.	I	1					
Definition: A finding of damage to Injury to superior vena cava	o the jugular vein. Asymptomatic diagnostic	Symptomatic; repair or revision	Severe symptoms; limiting self	Life-threatening consequences;	Death			
		Symptomatic; repair or revision not indicated	Severe symptoms; limiting self care ADL; disabling; repair or	Life-threatening consequences; evidence of end organ damage;	Death			
	Asymptomatic diagnostic	1 * '		evidence of end organ damage; urgent operative intervention	Death			
	Asymptomatic diagnostic finding; intervention not	1 * '	care ADL; disabling; repair or	evidence of end organ damage;	Death			
	Asymptomatic diagnostic finding; intervention not indicated	1 * '	care ADL; disabling; repair or	evidence of end organ damage; urgent operative intervention	Death			
Injury to superior vena cava	Asymptomatic diagnostic finding; intervention not indicated	1 * '	care ADL; disabling; repair or	evidence of end organ damage; urgent operative intervention	Death			
Injury to superior vena cava Definition: A finding of damage to	Asymptomatic diagnostic finding; intervention not indicated	not indicated	care ADL; disabling; repair or revision indicated	evidence of end organ damage; urgent operative intervention indicated				
Injury to superior vena cava Definition: A finding of damage to	Asymptomatic diagnostic finding; intervention not indicated the superior vena cava. Asymptomatic diagnostic	not indicated Symptomatic; medical	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic,	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences;				
Injury to superior vena cava Definition: A finding of damage to Intestinal stoma leak	Asymptomatic diagnostic finding; intervention not indicated the superior vena cava. Asymptomatic diagnostic observations only; intervention	not indicated Symptomatic; medical intervention indicated	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention				
Injury to superior vena cava Definition: A finding of damage to Intestinal stoma leak Definition: A finding of leakage of	Asymptomatic diagnostic finding; intervention not indicated the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated	not indicated Symptomatic; medical intervention indicated	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention				
Injury to superior vena cava Definition: A finding of damage to Intestinal stoma leak Definition: A finding of leakage of	Asymptomatic diagnostic finding; intervention not indicated the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (surgically created opening on the	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body).	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated	Death			
Injury to superior vena cava Definition: A finding of damage to Intestinal stoma leak	Asymptomatic diagnostic finding; intervention not indicated the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated	not indicated Symptomatic; medical intervention indicated (surgically created opening on the Self-limited; intervention not	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body). Severe symptoms; IV fluids,	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences;	Death			
Injury to superior vena cava Definition: A finding of damage to Intestinal stoma leak Definition: A finding of leakage of	Asymptomatic diagnostic finding; intervention not indicated the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated	not indicated Symptomatic; medical intervention indicated (surgically created opening on the Self-limited; intervention not	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body). Severe symptoms; IV fluids, tube feeding, or TPN indicated	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention	Death			
Injury to superior vena cava Definition: A finding of damage to Intestinal stoma leak Definition: A finding of leakage of Intestinal stoma obstruction	Asymptomatic diagnostic finding; intervention not indicated the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (surgically created opening on the Self-limited; intervention not indicated	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body). Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention	Death			
Injury to superior vena cava Definition: A finding of damage to Intestinal stoma leak Definition: A finding of leakage of Intestinal stoma obstruction	Asymptomatic diagnostic finding; intervention not indicated to the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated f contents from an intestinal stomatic diagnostic observations	Symptomatic; medical intervention indicated (surgically created opening on the Self-limited; intervention not indicated	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body). Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention	Death			
Injury to superior vena cava Definition: A finding of damage to Intestinal stoma leak Definition: A finding of leakage of Intestinal stoma obstruction Definition: A finding of blockage of Intestinal stoma obstruction	Asymptomatic diagnostic finding; intervention not indicated the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated f contents from an intestinal stomatic of the normal flow of the contents of the normal flow of the normal flow of the contents of the normal flow of the contents of the normal flow of the contents of the normal flow of the normal	Symptomatic; medical intervention indicated (surgically created opening on the Self-limited; intervention not indicated) of the intestinal stoma.	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body). Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated	Death			
Injury to superior vena cava Definition: A finding of damage to Intestinal stoma leak Definition: A finding of leakage of Intestinal stoma obstruction Definition: A finding of blockage of Intestinal stoma obstruction	Asymptomatic diagnostic finding; intervention not indicated to the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated f contents from an intestinal stomatic of the normal flow of the contents of the indicated for the normal flow of the contents of the indicated for the normal flow of the contents of the indicated for the normal flow of the contents of the indicated for the normal flow of the contents of the indicated for the indicated for the indicated flow of the contents of the indicated flow of the contents of the indicated flow of the contents of the indicated flow of the contents of the indicated flow of the contents of the indicated flow of the contents of the indicated flow of the contents of the indicated flow of the contents of the indicated flow of the contents of the indicated flow of the contents of the indicated flow of the contents of the indicated flow of the contents of the indicated flow of the contents of the indicated flow of the indicate	Symptomatic; medical intervention indicated (surgically created opening on the Self-limited; intervention not indicated of the intestinal stoma. Moderate bleeding; medical	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body). Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated Severe bleeding; transfusion	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A finding of damage to Intestinal stoma leak Definition: A finding of leakage of Intestinal stoma obstruction Definition: A finding of blockage of Intestinal stoma obstruction	Asymptomatic diagnostic finding; intervention not indicated be the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated f contents from an intestinal stomatic of the normal flow of the contents of the indicated for the normal flow of the contents of the indicated for the normal flow of the contents of the indicated for the normal flow of the contents of the indicated for the indicated flow of the contents of the indicated flow of the indicated flow of the contents of the indicated flow of the indicat	Symptomatic; medical intervention indicated (surgically created opening on the Self-limited; intervention not indicated of the intestinal stoma. Moderate bleeding; medical	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body). Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated Severe bleeding; transfusion indicated; radiologic or	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated	Death			
Injury to superior vena cava Definition: A finding of damage to Intestinal stoma leak Definition: A finding of leakage of Intestinal stoma obstruction Definition: A finding of blockage of Intestinal stoma site bleeding	Asymptomatic diagnostic finding; intervention not indicated to the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated of contents from an intestinal stomatic from the normal flow of the contents of the normal flow of the contents of the indicated on clinical exam; intervention not indicated	Symptomatic; medical intervention indicated (surgically created opening on the Self-limited; intervention not indicated of the intestinal stoma. Moderate bleeding; medical	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body). Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated Severe bleeding; transfusion indicated; radiologic or endoscopic intervention	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A finding of damage to Intestinal stoma leak Definition: A finding of leakage of Intestinal stoma obstruction Definition: A finding of blockage of Intestinal stoma site bleeding Definition: A finding of blood leak	Asymptomatic diagnostic finding; intervention not indicated to the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated of contents from an intestinal stomatic from the normal flow of the contents of the normal flow of the contents of the indicated on clinical exam; intervention not indicated	Symptomatic; medical intervention indicated (surgically created opening on the Self-limited; intervention not indicated of the intestinal stoma. Moderate bleeding; medical	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body). Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated Severe bleeding; transfusion indicated; radiologic or endoscopic intervention	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A finding of damage to Intestinal stoma leak Definition: A finding of leakage of Intestinal stoma obstruction Definition: A finding of blockage of Intestinal stoma site bleeding Definition: A finding of blood leak	Asymptomatic diagnostic finding; intervention not indicated the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated f contents from an intestinal stoma - of the normal flow of the contents of the normal flow of the contents on clinical exam; intervention not indicated age from the intestinal stoma.	Symptomatic; medical intervention indicated (surgically created opening on the Self-limited; intervention not indicated of the intestinal stoma. Moderate bleeding; medical intervention indicated	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body). Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated Complete resection or	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated	Death Death			
Injury to superior vena cava Definition: A finding of damage to Intestinal stoma leak Definition: A finding of leakage of Intestinal stoma obstruction Definition: A finding of blockage of Intestinal stoma obstruction	Asymptomatic diagnostic finding; intervention not indicated of the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated f contents from an intestinal stoma of the normal flow of the contents. Minimal bleeding identified on clinical exam; intervention not indicated indicated stage from the intestinal stoma.	Symptomatic; medical intervention indicated (surgically created opening on the Self-limited; intervention not indicated of the intestinal stoma. Moderate bleeding; medical intervention indicated	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body). Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated	Death Death			
njury to superior vena cava Definition: A finding of damage to ntestinal stoma leak Definition: A finding of leakage of ntestinal stoma obstruction Definition: A finding of blockage of ntestinal stoma site bleeding Definition: A finding of blood leak	Asymptomatic diagnostic finding; intervention not indicated the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated f contents from an intestinal stoma - of the normal flow of the contents of the normal flow of the contents on clinical exam; intervention not indicated age from the intestinal stoma.	Symptomatic; medical intervention indicated (surgically created opening on the Self-limited; intervention not indicated of the intestinal stoma. Moderate bleeding; medical intervention indicated	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body). Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated Complete resection or reconstruction of injured	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated	Death Death			
njury to superior vena cava Definition: A finding of damage to ntestinal stoma leak Definition: A finding of leakage of ntestinal stoma obstruction Definition: A finding of blockage of ntestinal stoma site bleeding Definition: A finding of blood leak ntraoperative arterial injury	Asymptomatic diagnostic finding; intervention not indicated the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated f contents from an intestinal stoma - of the normal flow of the contents of the normal flow of the contents on clinical exam; intervention not indicated age from the intestinal stoma. Primary repair of injured organ/structure indicated	Symptomatic; medical intervention indicated (surgically created opening on the Self-limited; intervention not indicated of the intestinal stoma. Moderate bleeding; medical intervention indicated Partial resection of injured organ/structure indicated	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body). Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated Complete resection or reconstruction of injured organ/structure indicated;	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated	Death Death			
Definition: A finding of damage to ntestinal stoma leak Definition: A finding of leakage of ntestinal stoma obstruction Definition: A finding of blockage of ntestinal stoma site bleeding Definition: A finding of blood leak ntraoperative arterial injury	Asymptomatic diagnostic finding; intervention not indicated the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated f contents from an intestinal stoma - of the normal flow of the contents of the normal flow of the contents are indicated on clinical exam; intervention not indicated age from the intestinal stoma. Primary repair of injured organ/structure indicated an artery during a surgical processor.	Symptomatic; medical intervention indicated (surgically created opening on the Self-limited; intervention not indicated of the intestinal stoma. Moderate bleeding; medical intervention indicated Partial resection of injured organ/structure indicated	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body). Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated Complete resection or reconstruction of injured organ/structure indicated; disabling	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent intervention indicated Life-threatening consequences; urgent intervention indicated	Death Death Death			
njury to superior vena cava Definition: A finding of damage to ntestinal stoma leak Definition: A finding of leakage of ntestinal stoma obstruction Definition: A finding of blockage of ntestinal stoma site bleeding Definition: A finding of blood leak ntraoperative arterial injury	Asymptomatic diagnostic finding; intervention not indicated the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated f contents from an intestinal stoma - of the normal flow of the contents of the normal flow of the contents from an intestinal stoma dinicated with the contents of the normal flow of the normal flow of the n	Symptomatic; medical intervention indicated (surgically created opening on the Self-limited; intervention not indicated of the intestinal stoma. Moderate bleeding; medical intervention indicated Partial resection of injured organ/structure indicated dure. Partial resection of injured	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body). Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated Complete resection or reconstruction of injured organ/structure indicated; disabling	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent intervention indicated Life-threatening consequences; urgent intervention indicated	Death Death			
Definition: A finding of damage to ntestinal stoma leak Definition: A finding of leakage of ntestinal stoma obstruction Definition: A finding of blockage of ntestinal stoma site bleeding Definition: A finding of blood leak ntraoperative arterial injury	Asymptomatic diagnostic finding; intervention not indicated the superior vena cava. Asymptomatic diagnostic observations only; intervention not indicated f contents from an intestinal stoma - of the normal flow of the contents of the normal flow of the contents are indicated on clinical exam; intervention not indicated age from the intestinal stoma. Primary repair of injured organ/structure indicated an artery during a surgical processor.	Symptomatic; medical intervention indicated (surgically created opening on the Self-limited; intervention not indicated of the intestinal stoma. Moderate bleeding; medical intervention indicated Partial resection of injured organ/structure indicated	care ADL; disabling; repair or revision indicated Severe symptoms; radiologic, endoscopic or elective operative intervention indicated e surface of the body). Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated Complete resection or reconstruction of injured organ/structure indicated; disabling	evidence of end organ damage; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent operative intervention indicated Life-threatening consequences; urgent intervention indicated Life-threatening consequences; urgent intervention indicated	Death Death Death			

			Grade		
Adverse Event	1	2	3	4	5
Definition: A finding of damage to	the breast parenchyma during a	surgical procedure.		•	•
Intraoperative cardiac injury	-	-	Primary repair of injured organ/structure indicated	Life-threatening consequences; urgent intervention indicated	Death
	the heart during a surgical proce				
Intraoperative ear injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection of injured organ/structure indicated; disabling (e.g., impaired hearing; impaired balance)	Life-threatening consequences; urgent intervention indicated	Death
	the ear during a surgical procedu				
Intraoperative endocrine injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to	the endocrine gland during a sur	gical procedure.			
Intraoperative gastrointestinal injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to	the gastrointestinal system durin	g a surgical procedure.			
Intraoperative head and neck injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to	the head and neck during a surg	ical procedure.			
Intraoperative hemorrhage	-	-	Postoperative radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of uncontrolled	ed bleeding during a surgical proc	edure.	•	•	•
Intraoperative hepatobiliary injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to	the hepatic parenchyma and/or b	oiliary tract during a surgical pro	cedure.		
Intraoperative musculoskeletal injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
	the musculoskeletal system duri		T	T	
Intraoperative neurological injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
	the nervous system during a sur			T	I
Intraoperative ocular injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to	the eye during a surgical proced	ure.		1	
Intraoperative renal injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to	the kidney during a surgical proc	edure.	•	•	,
Intraoperative reproductive tract injury		Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured	Life-threatening consequences; urgent intervention indicated	Death

Grade							
Adverse Event	1	2	3	4	5		
	the reproductive organs during a	surgical procedure.					
ntraoperative respiratory injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A finding of damage to	the respiratory system during a s	surgical procedure.	1	1			
Intraoperative skin injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A finding of damage to	the skin during a surgical proced	ure.					
Intraoperative splenic injury	the poleon during a gurgical pro-	Primary repair of injured organ/structure indicated	Resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death		
	the spleen during a surgical prod		Complete resection or	Life threatening concessions	Dooth		
Intraoperative urinary injury Definition: A finding of damage to	Primary repair of injured organ/structure indicated organ/structure indicated or the urinary system during a surg	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death		
		Partial resection of injured	Complete resection or	Life threatening consequences:	Death		
Intraoperative venous injury	Primary repair of injured organ/structure indicated	organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Deam		
Definition: A finding of damage to	a vein during a surgical procedu	re.					
Kidney anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A finding of leakage of	furine due to breakdown of a kidn	ey anastomosis (surgical connect	on of two separate anatomic struc	tures).			
Large intestinal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death		
Definition: A finding of leakage du	ue to breakdown of an anastomos	is (surgical connection of two sepa	arate anatomic structures) in the la	arge intestine.			
Pancreatic anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	indicated	Death		
			f two separate anatomic structure	ĺ			
Pharyngeal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	indicated	Death		
		, ,	of two separate anatomic structure	1	1_		
Postoperative hemorrhage Definition: A finding of bleeding o	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; radiologic, endoscopic, or operative intervention indicated	Transfusion indicated of >=2 units (10 cc/kg for pediatrics) pRBCs beyond protocol specification; urgent radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
	and a surgical procedure	Extubated within 24 - 72 hrs	Extubated >72 hrs	Life threatening simusu	Death		
Postoperative thoracic procedure complication	-	Extubated within 24 - 72 hrs postoperatively	Extubated >72 hrs postoperatively, but before tracheostomy indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death		
	ly undocumented problem that oc		T	T			
Prolapse of intestinal stoma	Asymptomatic; reducible	Recurrent after manual reduction; local irritation or stool leakage; difficulty to fit appliance; limiting instrumental ADL	Severe symptoms; elective operative intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death		

			Grade		
Adverse Event	1	2	3	4	5
Definition: A finding of protrusion	of the intestinal stoma (surgically	created opening on the surface of	the body) above the abdominal s	urface.	
Prolapse of urostomy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Local care or maintenance; minor revision indicated	Dysfunctional stoma; elective operative intervention or major stomal revision indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of displacem	ent of the urostomy.				
Radiation recall reaction (dermatologic)	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death
-	inflammatory reaction caused by		-	lowing radiotherapy. The inflamma	tory react
· · · · · · · · · · · · · · · · · · ·	liated skin and the symptoms disa	i i			
Rectal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage d	ue to breakdown of a rectal anasto	omosis (surgical connection of two	separate anatomic structures).	T	
Seroma	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; simple aspiration indicated	Symptomatic, elective radiologic or operative intervention indicated	-	-
Definition: A finding of tumor-like	collection of serum in the tissues.		1	1	
Small intestinal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage d	ue to breakdown of an anastomos	is (surgical connection of two sepa	arate anatomic structures) in the si	mall bowel.	
Spermatic cord anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage d	ue to breakdown of a spermatic co	ord anastomosis (surgical connecti	on of two separate anatomic struc	tures).	
Spinal fracture	Mild back pain; nonprescription analgesics indicated	Moderate back pain; prescription analgesics indicated; limiting instrumental ADL	Severe back pain; hospitalization or intervention indicated for pain control (e.g., vertebroplasty); limiting self care ADL; disability	Life-threatening consequences; symptoms associated with neurovascular compromise	Death
Definition: A finding of traumatic	injury to the spine in which the cor	itinuity of a vertebral bone is broke	en.	<u>!</u>	•
Stenosis of gastrointestinal stoma	-	Symptomatic; IV fluids indicated <24 hrs; manual dilation at bedside	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
	of the gastrointestinal stoma (surg				
Stomal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characteriz	ed by a circumscribed, inflammato	ory and necrotic erosive lesion on t	he jejunal mucosal surface close t	to the anastomosis site following a	
Tracheal hemorrhage	Minimal bleeding identified on	Moderate bleeding; medical	Severe bleeding; transfusion	Life-threatening consequences;	Death
v	clinical or diagnostic exam; intervention not indicated	intervention indicated	indicated; radiologic or endoscopic intervention indicated	urgent intervention indicated	
Definition: A finding of bleeding f		I .	Ī.	T .	
Tracheal obstruction	Partial asymptomatic obstruction on examination (e.g., visual, radiologic or endoscopic)	Symptomatic (e.g., noisy airway breathing), no respiratory distress; medical intervention indicated (e.g., steroids); limiting	Stridor; radiologic or endoscopic intervention indicated (e.g., stent, laser); limiting self care ADL	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death

Injury, poisoning and procedural complications								
			Grade					
Adverse Event	1	2	3	4	5			
Tracheostomy site bleeding	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A finding of blood leal	kage from the tracheostomy site.							
Ureteric anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
	lue to breakdown of a ureteral ana	stomosis (surgical connection of to						
Jrethral anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A finding of leakage d	lue to breakdown of a urethral ana	stomosis (surgical connection of to	vo separate anatomic structures).					
Urostomy leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A finding of leakage o	of contents from a urostomy.	T	Т	T				
Urostomy obstruction	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; dilation or endoscopic repair or stent placement indicated	Altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); elective operative intervention indicated	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death			
Definition: A finding of blockage	of the urostomy.							
Urostomy site bleeding	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A finding of bleeding t	from the urostomy site.	1	'	'	•			
Urostomy stenosis	-	Symptomatic but no hydronephrosis, no sepsis or no renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic (e.g., hydronephrosis, or renal dysfunction); elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A finding of narrowing	of the opening of a urostomy.	1-	'	,	•			
Uterine anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A finding of leakage d	lue to breakdown of a uterine anas	tomosis (surgical connection of tw	o separate anatomic structures).					
Uterine perforation	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
	zed by a rupture in the uterine wall.	T.						
√aginal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A finding of leakage d	lue to breakdown of a vaginal anas	tomosis (surgical connection of tw	vo separate anatomic structures).	Γ				
/as deferens anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A finding of leakage d	lue to breakdown of a vas deferens	s anastomosis (surgical connection	n of two separate anatomic structu	res).				
Vascular access complication	-	Device dislodgement, blockage, leak, or malposition; device replacement indicated	Deep vein or cardiac thrombosis; intervention indicated (e.g., anticoagulation, lysis, filter, invasive procedure)	Embolic event including pulmonary embolism or life- threatening thrombus	Death			

	Injury	, poisoning and procedu	ral complications		
			Grade		
Adverse Event	1	2	3	4	5
Venous injury	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); repair or revision not indicated	Severe symptoms; limiting self care ADL; repair or revision indicated; disabling	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to	a vein.				
Wound complication	Incisional separation of <=25% of wound, no deeper than superficial fascia	Incisional separation >25% of wound; local care indicated	Hernia without evidence of strangulation; fascial disruption/dehiscence; primary wound closure or revision by operative intervention indicated	Hernia with evidence of strangulation; major reconstruction flap, grafting, resection, or amputation indicated	Death
· · · · · ·	Incisional separation of <=25%	1	Fascial disruption or dehiscence	Life threatening concessions	Dooth
Wound dehiscence	Incisional separation of <=25% of wound, no deeper than superficial fascia	Incisional separation >25% of wound with local care; asymptomatic hernia or symptomatic hernia without evidence of strangulation	Hascial disruption or deniscence without evisceration; primary wound closure or revision by operative intervention indicated	Life-threatening consequences; symptomatic hernia with evidence of strangulation; fascial disruption with evisceration; major reconstruction flap, grafting, resection, or amputation indicated	Death
Definition: A finding of separation	of the approximated margins of a	surgical wound.	T	Г	1
Wrist fracture	Mild; non-surgical intervention indicated	Limiting instrumental ADL; operative intervention indicated	Limiting self care ADL; elective surgery indicated	-	-
Definition: A finding of traumatic	injury to the wrist joint in which the	continuity of a wrist bone is broke	en.		
Injury, poisoning and procedural complications - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

		Investigations	5		
			Grade		
Adverse Event	1	2	3	4	5
Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage	-	-
	•		reater than the control value. As a	possible indicator of coagulopat	thy, a prolonged
, ,	may occur in a variety of disease	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	
Alanine aminotransferase increased					-
	1		minotransferase (ALT or SGPT) in	1	
Alkaline phosphatase increased	ı	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Aspartate aminotransferase increased	oratory test results that indicate a	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
	l poratory test results that indicate a	l n increase in the level of aspartate	I e aminotransferase (AST or SGOT	l i) in a blood specimen	ı
Blood antidiuretic hormone abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Hospitalization indicated	-	-
Definition: A finding based on lab	oratory test results that indicate a	bnormal levels of antidiuretic horm	none in the blood specimen.		
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN	-
Definition: A finding based on lab	oratory test results that indicate a	n abnormally high level of bilirubin	in the blood. Excess bilirubin is a	ssociated with jaundice.	
Blood corticotrophin decreased	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Hospitalization indicated	-	-
Definition: A finding based on lab	oratory test results that indicate a	n decrease in levels of corticotrop	hin in a blood specimen.	1	
Blood gonadotrophin abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A finding based on lab	oratory test results that indicate a	, bnormal levels of gonadotrophin h	ormone in a blood specimen.	'	'
Blood prolactin abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	-	-	-
Definition: A finding based on lab	oratory test results that indicate a	l bnormal levels of prolactin hormor	l ne in a blood specimen	I .	l
Carbon monoxide diffusing capacity decreased	3 - 5 units below LLN; for follow- up, a decrease of 3 - 5 units (ml/min/mm Hg) below the baseline value	6 - 8 units below LLN; for follow- up, an asymptomatic decrease of >5 - 8 units (ml/min/mm Hg) below the baseline value	Asymptomatic decrease of >8 units drop; >5 units drop along with the presence of pulmonary symptoms (e.g., >Grade 2 hypoxia or >Grade 2 or higher dyspnea)	-	-
Definition: A finding based on lun	g function test results that indicate	a decrease in the lung capacity	to absorb carbon monoxide.		·
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer	-	-
Definition: A laboratory test resul	t which indicates increased levels	of cardiac troponin I in a biologica	I specimen.	T	
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer	-	-
Definition: A laboratory test resul	t which indicates increased levels	of cardiac troponin T in a biologica	al specimen.	Т	
CD4 lymphocytes decreased	<lln -="" 0.5="" 500="" <lln="" mm3;="" x<br="">10e9 /L</lln>	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200 - 50/mm3; <0.2 x 0.05 - 10e9 /L	<50/mm3; <0.05 x 10e9 /L	-
Definition: A finding based on lab	oratory test results that indicate a			T	
Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L	-
Definition: A finding based on lab	oratory test results that indicate h	igher than normal levels of choles	terol in a blood specimen.	T	
CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN osphokinase in a blood specimen.	>10 x ULN	-

		Investigations	•		
			Grade		
Adverse Event	1	2	3	4	5
Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	-
Definition: A finding based on lab	oratory test results that indicate in	creased levels of creatinine in a b	iological specimen.		
Ejection fraction decreased	-	Resting ejection fraction (EF) 50 - 40%; 10 - 19% drop from baseline	Resting ejection fraction (EF) 39 - 20%; >20% drop from baseline	. ,	-
Definition: The percentage comp contraction.	uted when the amount of blood ejo	ected during a ventricular contracti	on of the heart is compared to the	amount that was present prior to	the
Electrocardiogram QT corrected interval prolonged		QTc 481 - 500 ms	QTc >= 501 ms on at least two separate ECGs	QTc >= 501 or >60 ms change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	-
	dysrhythmia characterized by an a			.0.05	
Fibrinogen decreased	<1.0 - 0.75 x LLN or <25% decrease from baseline	<0.75 - 0.5 x LLN or 25 - <50% decrease from baseline	<0.5 - 0.25 x LLN or 50 - <75% decrease from baseline	<0.25 x LLN or 75% decrease from baseline or absolute value <50 mg/dL	-
Definition: A finding based on lab	oratory test results that indicate a	n decrease in levels of fibrinogen i	n a blood specimen.		
Forced expiratory volume decreased	FEV1% (percentages of observed FEV1 and FVC related to their respective predicted values) 99 - 70% predicted	FEV1 60 - 69%	50 - 59%	<= 49%	-
Definition: A finding based on tes	st results that indicate a relative de	crease in the fraction of the forced	l vital capacity that is exhaled in a	specific number of seconds.	
-	>ULN - 2.5 x ULN poratory test results that indicate h	-			- nma-
	he transfer of a gamma glutamyl g T		ide to another peptide, amino acid I	s or water.	
Growth hormone abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	-	-	-
Definition: A finding based on lab	oratory test results that indicate a	bnormal levels of growth hormone	in a biological specimen.		
Haptoglobin decreased	<lln< td=""><td>-</td><td>-</td><td>-</td><td>-</td></lln<>	-	-	-	-
Definition: A finding based on lab	oratory test results that indicate a	n decrease in levels of haptoglobir	n in a blood specimen.		
Hemoglobin increased	Increase in >0 - 2 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN	-	-
Definition: A finding based on lab	oratory test results that indicate in	creased levels of hemoglobin in a	biological specimen.	Г	1
INR increased	>1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation	-	-
Definition: A finding based on lab	oratory test results that indicate a	n increase in the ratio of the patier	nt's prothrombin time to a control s	ample in the blood.	
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN	-
Definition: A finding based on lab	oratory test results that indicate a	n increase in the level of lipase in	a biological specimen.	Т	
Lymphocyte count decreased	<pre><lln -="" 0.8="" 10e9="" 800="" <lln="" l<="" mm3;="" pre="" x=""></lln></pre>	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	-
	oratory test results that indicate a				
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	l -
Definition: A finding based on lab Neutrophil count decreased		<1500 - 1000/mm3; <1.5 - 1.0 x	<1000 - 500/mm3; <1.0 - 0.5 x	sions or bone marrow. <500/mm3; <0.5 x 10e9 /L	-
	10e9 /L	10e9 /L	10e9 /L		1
Definition: A finding based on lab Pancreatic enzymes decreased	coratory test results that indicate a	Increase in stool frequency,	Sequelae of absorption	-	-
Definition: A finding based on lab	oratory test results that indicate a	bulk, or odor; steatorrhea n decrease in levels of pancreatic	deficiency enzymes in a biological specimen	<u> </u>	l

		Investigations			
			Grade		
Adverse Event	1	2	3	4	5
Platelet count decreased	<lln -="" -<="" 75,000="" <lln="" mm3;="" td=""><td><75,000 - 50,000/mm3; <75.0 -</td><td><50,000 - 25,000/mm3; <50.0 -</td><td><25,000/mm3; <25.0 x 10e9 /L</td><td>-</td></lln>	<75,000 - 50,000/mm3; <75.0 -	<50,000 - 25,000/mm3; <50.0 -	<25,000/mm3; <25.0 x 10e9 /L	-
	75.0 x 10e9 /L	50.0 x 10e9 /L	25.0 x 10e9 /L		
Definition: A finding based on lab	poratory test results that indicate a	decrease in number of platelets in	a blood specimen.		
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN	
Definition: A finding based on lab	oratory test results that indicate a	n increase in the levels of amylase	in a serum specimen.		
Urine output decreased	-	-	Oliguria (<80 ml in 8 hr)	Anuria (<240 ml in 24 hr)	-
Definition: A finding based on tes	st results that indicate urine produc	tion is less relative to previous ou	tput.	•	,
Vital capacity abnormal	90 - 75% of predicted value	<75 - 50% of predicted value;	<50% of predicted value;	=	-
		limiting instrumental ADL	limiting self care ADL		
Definition: A finding based on pu	lmonary function test results that in	ndicate an abnormal vital capacity	(amount of exhaled after a maxim	um inhalation) when compared to	the predicted
value.	T	T		T	1
Weight gain	5 - <10% from baseline	10 - <20% from baseline	>=20% from baseline	-	-
Definition: A finding characterize	d by an increase in overall body w	eight; for pediatrics, greater than t	he baseline growth curve.		
Weight loss	5 to <10% from baseline;	10 - <20% from baseline;	>=20% from baseline; tube	-	-
	intervention not indicated	nutritional support indicated	feeding or TPN indicated		
Definition: A finding characterize	d by a decrease in overall body we	eight; for pediatrics, less than the b	paseline growth curve.		
White blood cell decreased	<lln -="" 3.0="" 3000="" <lln="" mm3;="" td="" x<=""><td><3000 - 2000/mm3; <3.0 - 2.0 x</td><td><2000 - 1000/mm3; <2.0 - 1.0 x</td><td><1000/mm3; <1.0 x 10e9 /L</td><td>-</td></lln>	<3000 - 2000/mm3; <3.0 - 2.0 x	<2000 - 1000/mm3; <2.0 - 1.0 x	<1000/mm3; <1.0 x 10e9 /L	-
	10e9 /L	10e9 /L	10e9 /L		
Definition: A finding based on lab	poratory test results that indicate a	n decrease in number of white blo	od cells in a blood specimen.	·	
Investigations - Other, specify	Asymptomatic or mild	Moderate; minimal, local or	Severe or medically significant	Life-threatening consequences;	Death
	, , ,	noninvasive intervention	but not immediately life-	urgent intervention indicated	
	observations only; intervention	indicated; limiting age-	threatening; hospitalization or		
	not indicated	appropriate instrumental ADL	prolongation of existing		
			hospitalization indicated;		
			disabling; limiting self care ADL		

		Metabolism and nutrition	n disorders		
			Grade		
Adverse Event	1	2	3	4	5
cidosis	pH <normal, but="">=7.3</normal,>	-	pH <7.3	Life-threatening consequences	Death
efinition: A disorder characteri:	zed by abnormally high acidity (high	h hydrogen-ion concentration) of t	he blood and other body tissues.		
Alcohol intolerance	-	Present	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteri: omiting, indigestion and heada	zed by an increase in sensitivity to	the adverse effects of alcohol, wh	ich can include nasal congestion,	skin flushes, heart dysrhythmias,	nausea,
Alkalosis	pH >normal, but <=7.5		pH >7.5	Life-threatening consequences	Death
		-	1.	Life-tiffeaterining consequences	Death
	zed by abnormally high alkalinity (lo			Life 45	D41-
Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteria	zed by a loss of appetite.	,	,	·	
Dehydration	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated <24 hrs	IV fluids or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteria	zed by excessive loss of water from	n the body. It is usually caused by	severe diarrhea, vomiting or diaph	noresis.	
Glucose intolerance	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; dietary modification or oral agent indicated	Severe symptoms; insulin indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	zed by an inability to properly meta	bolize glucose.			
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; lonized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; lonized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; lonized calcium >1.8 mmol/L; life-threatening consequences	Death
Definition: A disorder characteria	zed by laboratory test results that ir	, ndicate an elevation in the concen	ration of calcium (corrected for all	oumin) in blood.	•
Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life- threatening consequences	Death
Definition: A disorder characteri: ntolerance.	zed by laboratory test results that in	ndicate an elevation in the concen	tration of blood sugar. It is usually	an indication of diabetes mellitus	or glucose
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences	Death
Definition: A disorder characteri: he use of diuretic drugs.	zed by laboratory test results that ir	ndicate an elevation in the concen	tration of potassium in the blood; a	associated with kidney failure or so	ometimes w
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences	Death
Definition: A disorder characteria	zed by laboratory test results that in	ndicate an elevation in the concen	tration of magnesium in the blood	T	
lypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death
Definition: A disorder characteria	zed by laboratory test results that in	ndicate an elevation in the concen	tration of sodium in the blood.	Τ	T
lypertriglyceridemia	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L; life-threatening consequences	Death
efinition: A disorder characteriz	zed by laboratory test results that in	ndicate an elevation in the concen	tration of triglyceride concentration	n in the blood.	1
lyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences	>10 mg/dL; >0.59 mmol/L; life- threatening consequences	Death
efinition: A disorder characteri:	zed by laboratory test results that ir	ndicate an elevation in the concen	tration of uric acid.		
lypoalbuminemia	<lln -="" 3="" 30="" <lln="" dl;="" g="" l<="" td=""><td><3 - 2 g/dL; <30 - 20 g/L</td><td><2 g/dL; <20 g/L</td><td>Life-threatening consequences; urgent intervention indicated</td><td>Death</td></lln>	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated	Death
efinition: A disorder characteri:	zed by laboratory test results that ir	ndicate a low concentration of albu	ımin in the blood.		

		Metabolism and nutrition	n disorders		
			Grade		
Adverse Event	1	2	3	4	5
Hypocalcemia	Corrected serum calcium of <lln -="" 2.0<br="" 8.0="" <lln="" dl;="" mg="">mmol/L; lonized calcium <lln -<br="">1.0 mmol/L</lln></lln>	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; lonized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; lonized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; Iife-threatening consequences	Death
Definition: A disorder characterize	ed by laboratory test results that ir	ndicate a low concentration of calc	ium (corrected for albumin) in the	blood.	,
Hypoglycemia	<lln -="" 3.0="" 55="" <lln="" dl;="" l<="" mg="" mmol="" td=""><td><55 - 40 mg/dL; <3.0 - 2.2 mmol/L</td><td><40 - 30 mg/dL; <2.2 - 1.7 mmol/L</td><td><30 mg/dL; <1.7 mmol/L; life- threatening consequences; seizures</td><td>Death</td></lln>	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life- threatening consequences; seizures	Death
Definition: A disorder characteriz	ed by laboratory test results that in	ndicate a low concentration of gluc	ose in the blood.		
Hypokalemia	<lln -="" 3.0="" l<="" mmol="" td=""><td><lln -="" 3.0="" l;<br="" mmol="">symptomatic; intervention indicated</lln></td><td><3.0 - 2.5 mmol/L; hospitalization indicated</td><td><2.5 mmol/L; life-threatening consequences</td><td>Death</td></lln>	<lln -="" 3.0="" l;<br="" mmol="">symptomatic; intervention indicated</lln>	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death
Definition: A disorder characteriz	ed by laboratory test results that ir	ndicate a low concentration of pota	assium in the blood.		
Hypomagnesemia	<lln -="" 0.5="" 1.2="" <lln="" dl;="" l<="" mg="" mmol="" td=""><td><1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L</td><td><0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L</td><td><0.7 mg/dL; <0.3 mmol/L; life-threatening consequences</td><td>Death</td></lln>	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; life-threatening consequences	Death
Definition: A disorder characteriz	ed by laboratory test results that in	ndicate a low concentration of mag	nesium in the blood.		
Hyponatremia	<lln -="" 130="" l<="" mmol="" td=""><td>-</td><td><130 - 120 mmol/L</td><td><120 mmol/L; life-threatening consequences</td><td>Death</td></lln>	-	<130 - 120 mmol/L	<120 mmol/L; life-threatening consequences	Death
Definition: A disorder characteriz	ed by laboratory test results that ir	ndicate a low concentration of sod	um in the blood.		
Hypophosphatemia	<lln -="" 0.8="" 2.5="" <lln="" dl;="" l<="" mg="" mmol="" td=""><td><2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L</td><td><2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L</td><td><1.0 mg/dL; <0.3 mmol/L; life- threatening consequences</td><td>Death</td></lln>	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L	<1.0 mg/dL; <0.3 mmol/L; life- threatening consequences	Death
Definition: A disorder characteriz	ed by laboratory test results that in	ndicate a low concentration of pho	sphates in the blood.		
Iron overload	-	Moderate symptoms; intervention not indicated	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by accumulation of iron in the ti	issues.			
Obesity	-	BMI 25 - 29.9 kg/m2	BMI 30 - 39.9 kg/m2	BMI >=40 kg/m2	-
Definition: A disorder characteriz	ed by having a high amount of boo	dy fat.			
Tumor lysis syndrome	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by metabolic abnormalities that	t result from a spontaneous or the	rapy-related cytolysis of tumor cell	S	
Metabolism and nutrition disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

	Muscu	loskeletal and connectiv	e tissue disorders					
	Grade							
Adverse Event	1	2	3	4	5			
Abdominal soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g. tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteriz	ed by a necrotic process occurring	in the soft tissues of the abdomir	nal wall.					
Arthralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characteriz	red by a sensation of marked disco	omfort in a joint.	1	Ī				
Arthritis	Mild pain with inflammation, erythema, or joint swelling	Moderate pain associated with signs of inflammation, erythema, or joint swelling; limiting instrumental ADL	Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self care ADL	-	-			
Definition: A disorder characteriz	ed by inflammation involving a join	nt.	1	1				
Avascular necrosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
	ted by necrotic changes in the boned the destruction of the bone struction and the bone struction.		od supply. Most often affecting the	epiphysis of the long bones, the n	ecrotic			
Back pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characteriz	ed by marked discomfort sensation	n in the back region.						
Bone pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characteriz	ed by marked discomfort sensatio	n in the bones.	T	T				
Buttock pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characteriz	ed by marked discomfort sensation	n in the buttocks.						
Chest wall pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characterize	ed by marked discomfort sensation	n in the chest wall region.						
Exostosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	-	-			
Definition: A disorder characteriz	ed by non-neoplastic overgrowth	of bone.						
Fibrosis deep connective tissue	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration; unable to slide or pinch skin; limiting joint or orifice movement (e.g. mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death			
Definition: A disorder characteriz	ed by fibrotic degeneration of the	deep connective tissues.	1	T	1			
Flank pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characterize	ed by marked discomfort sensation	n on the lateral side of the body in	the region below the ribs and abo	ve the hip.				
Generalized muscle weakness	Symptomatic; weakness perceived by patient but not evident on physical exam	Symptomatic; weakness evident on physical exam; weakness limiting instrumental ADL	Weakness limiting self care ADL; disabling	-	-			
Definition: A disorder characteriz	red by a reduction in the strength o	of muscles in multiple anatomic sit	es.	T				
Growth suppression	Reduction in growth velocity by 10 - 29% ideally measured over the period of a year	Reduction in growth velocity by 30 - 49% ideally measured over the period of a year or 0 - 49% reduction in growth from the baseline growth curve	Reduction in growth velocity of >=50% ideally measured over the period of a year	-	-			

Musculoskeletal and connective tissue disorders Grade								
Advance Event	1	2	3	4	5			
Adverse Event Head soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteriz	ed by a necrotic process occurring	in the soft tissues of the head.						
Joint effusion	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated; disabling	-	-			
Definition: A disorder characteriz	ed by excessive fluid in a joint, usu	ually as a result of joint inflammati	on.	T				
Joint range of motion decreased	<=25% loss of ROM (range of motion); decreased ROM limiting athletic activity	>25 - 50% decrease in ROM; limiting instrumental ADL	>50% decrease in ROM; limiting self care ADL; disabling	-	-			
Definition: A disorder characteriz	ed by a decrease in joint flexibility	of any joint.						
Joint range of motion decreased cervical spine	Mild restriction of rotation or flexion between 60 - 70 degrees	Rotation <60 degrees to right or left; <60 degrees of flexion	Ankylosed/fused over multiple segments with no C-spine rotation	-	-			
Definition: A disorder characteriz	ed by a decrease in flexibility of a	cervical spine joint.	I	T				
Joint range of motion decreased lumbar spine	Stiffness; difficulty bending to the floor to pick up a very light object but able to do athletic activity	Pain with range of motion (ROM) in lumbar spine; requires a reaching aid to pick up a very light object from the floor	<50% lumbar spine flexion; associated with symptoms of ankylosis or fused over multiple segments with no L-spine flexion (e.g., unable to reach to floor to pick up a very light object)	-	-			
Definition: A disorder characteriz	ed by a decrease in flexibility of a	lumbar spine joint.						
Kyphosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate accentuation; limiting instrumental ADL	Severe accentuation; operative intervention indicated; limiting self care ADL	-	-			
Definition: A disorder characteriz	ed by an abnormal increase in the	curvature of the thoracic portion of	of the spine.					
Lordosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate accentuation; limiting instrumental ADL	Severe accentuation; operative intervention indicated; limiting self care ADL	-	-			
Definition: A disorder characteriz	ed by an abnormal increase in the	curvature of the lumbar portion of	the spine.					
Muscle weakness left-sided	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL; disabling	-	-			
Definition: A disorder characteriz	ed by a reduction in the strength o	f the muscles on the left side of th	e body.					
Muscle weakness lower limb	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL; disabling	-	-			
Definition: A disorder characteriz	ed by a reduction in the strength o	f the lower limb muscles.						
Muscle weakness right-sided	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL; disabling	-	-			
Definition: A disorder characteriz	ed by a reduction in the strength o	f the muscles on the right side of t	the body.	ı				
Muscle weakness trunk	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL; disabling	-	-			
		f the trunk muscles						
Definition: A disorder characteriz	ed by a reduction in the strength o	i tile tittik iliuscies.						

			Grade		
Adverse Event	1	2	3	4	5
Musculoskeletal deformity	Cosmetically and functionally insignificant hypoplasia	Deformity, hypoplasia, or asymmetry able to be remediated by prosthesis (e.g., shoe insert) or covered by clothing	Significant deformity, hypoplasia, or asymmetry, unable to be remediated by prosthesis or covered by clothing; disabling	-	-
Definition: A disorder character	ized by of a malformation of the mu	sculoskeletal system.			•
Myalgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder character	ized by marked discomfort sensatio	n originating from a muscle or gro	up of muscles.		
Myositis	Mild pain	Moderate pain associated with weakness; pain limiting instrumental ADL	Pain associated with severe weakness; limiting self care ADL	-	-
Definition: A disorder character	ized by inflammation involving the s	keletal muscles.			
Neck pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder character	ized by marked discomfort sensatio	n in the neck area.	т.	T	
Neck soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder character	ized by a necrotic process occurring	in the soft tissues of the neck.		_	
Osteonecrosis of jaw	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (e.g., topical agents); limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder character	zed by a necrotic process occurring	g in the bone of the mandible.			
Osteoporosis	Radiologic evidence of osteoporosis or Bone Mineral Density (BMD) t-score -1 to -2.5 (osteopenia); no loss of height or intervention indicated	BMD t-score <-2.5; loss of height <2 cm; anti-osteoporotic therapy indicated; limiting instrumental ADL	Loss of height >=2 cm; hospitalization indicated; limiting self care ADL	-	-
Definition: A disorder charactericomposition), resulting in increa	ized by reduced bone mass, with a ased fracture incidence.	decrease in cortical thickness and	in the number and size of the trab	peculae of cancellous bone (but no	ormal chei
Pain in extremity	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder character	zed by marked discomfort sensatio	n in the upper or lower extremities	b.		
Pelvic soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death
	ized by a necrotic process occurring	1	. 45 damas a		
Scoliosis	<20 degrees; clinically undetectable	>20 - 45 degrees; visible by forward flexion; limiting instrumental ADL	>45 degrees; scapular prominence in forward flexion; operative intervention indicated; limiting self care ADL; disabling	-	-
Definition: A disorder character	ized by a malformed, lateral curvatu	ire of the spine.			
Soft tissue necrosis lower limb	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder character	zed by a necrotic process occurring	in the soft tissues of the lower ex	tremity.		
Soft tissue necrosis upper limb	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death

	Muscu	loskeletal and connectiv	e tissue disorders					
	Grade							
Adverse Event	1	2	3	4	5			
Superficial soft tissue fibrosis	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration; unable to slide or pinch skin; limiting joint or orifice movement (e.g., mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death			
Definition: A disorder characterize	ed by fibrotic degeneration of the	superficial soft tissues.						
Trismus	Decreased ROM (range of motion) without impaired eating	Decreased ROM requiring small bites, soft foods or purees	Decreased ROM with inability to adequately aliment or hydrate orally	-	-			
Definition: A disorder characterize	ed by lack of ability to open the mo	outh fully due to a decrease in the	range of motion of the muscles of	mastication.	•			
Unequal limb length	Mild length discrepancy <2 cm	Moderate length discrepancy 2 - 5 cm; shoe lift indicated; limiting instrumental ADL	, ,	-	-			
Definition: A disorder characterize	ed by of a discrepancy between th	e lengths of the lower or upper ex	tremities.					
Musculoskeletal and connective tissue disorder - Other, specify	' '	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death			

	Neoplasms benig	n, malignant and unspec	cified (incl cysts and poly	yps)				
	Grade							
Adverse Event	1	2	3	4	5			
Leukemia secondary to oncology chemotherapy	-	-	-	Present	Death			
Definition: A disorder characterize	ed by leukemia arising as a result	of the mutagenic effect of chemot	herapy agents.					
Myelodysplastic syndrome	-	-	-	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characterize	ed by insufficiently healthy hemata	poietic cell production by the bone	e marrow.					
Treatment related secondary malignancy	-	-	Non life-threatening secondary malignancy	Acute life-threatening secondary malignancy; blast crisis in leukemia	Death			
Definition: A disorder characterize	ed by development of a malignand	by most probably as a result of trea	atment for a previously existing ma	alignancy.				
Tumor pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characterize	ed by marked discomfort from a ne	eoplasm that may be pressing on	a nerve, blocking blood vessels, ir	nflamed or fractured from metastas	sis.			
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death			

Definition: A disorder characterized by Accessory nerve disorder Definition: A disorder characterized by Accustic nerve disorder NOS Accustic nerve disorder NOS Accustic nerve disorder NOS Accustic nerve disorder NOS Accustic nerve disorder characterized by Accustic nerve disorder characterized by Akathisia Definition: A disorder characterized by Amnesia Definition: A disorder characterized by Aphonia	symptomatic; clinical or agnostic observations only; tervention not indicated by involvement of the accessor agnostic observations only; tervention not indicated by involvement of the acoustic observations only; tervention not indicated by involvement of the acoustic observations or increased of a country of the acoustic of the accessor of the acce	Moderate symptoms; limiting instrumental ADL y nerve (eleventh cranial nerve). Moderate symptoms; limiting instrumental ADL nerve (eighth cranial nerve). Moderate restlessness or increased motor activity; limiting instrumental ADL		-	-
Abducens nerve disorder Asy diag inte Definition: A disorder characterized by Accessory nerve disorder Asy diag inte Definition: A disorder characterized by Acoustic nerve disorder NOS Asy diag inte Definition: A disorder characterized by Akathisia Definition: A disorder characterized by Amnesia Mild Definition: A disorder characterized by Aphonia Definition: A disorder characterized by Aphonia Definition: A disorder characterized by Aphonia Definition: A disorder characterized by Aphonia	symptomatic; clinical or agnostic observations only; tervention not indicated by involvement of the abducent agnostic observations only; tervention not indicated by involvement of the accessor agnostic observations only; tervention not indicated by involvement of the accessor agnostic observations only; tervention not indicated by involvement of the acoustic observations only; tervention not indicated by involvement of the acoustic or increased of the accustic of the accust	Moderate symptoms; limiting instrumental ADL s nerve (sixth cranial nerve). Moderate symptoms; limiting instrumental ADL y nerve (eleventh cranial nerve). Moderate symptoms; limiting instrumental ADL nerve (eighth cranial nerve). Moderate restlessness or increased motor activity; limiting instrumental ADL	Severe symptoms; limiting self care ADL Severe symptoms; limiting self care ADL Severe symptoms; limiting self care ADL Severe restlessness or increased motor activity; limiting	-	-
Definition: A disorder characterized by Accessory nerve disorder Definition: A disorder characterized by Accessory nerve disorder Definition: A disorder characterized by Accessory nerve disorder NOS Accessory nerve disorder characterized by Accessory nerve disorder characterized by Accessory nerve disorder nos Accessory nerve diso	agnostic observations only; tervention not indicated by involvement of the abducens symptomatic; clinical or agnostic observations only; tervention not indicated by involvement of the accessor symptomatic; clinical or agnostic observations only; tervention not indicated by involvement of the accustic observations only; tervention not indicated by involvement of the acoustic of lid restlessness or increased other activity.	instrumental ADL s nerve (sixth cranial nerve). Moderate symptoms; limiting instrumental ADL y nerve (eleventh cranial nerve). Moderate symptoms; limiting instrumental ADL nerve (eighth cranial nerve). Moderate restlessness or increased motor activity; limiting instrumental ADL	care ADL Severe symptoms; limiting self care ADL Severe symptoms; limiting self care ADL Severe restlessness or increased motor activity; limiting	-	-
Accessory nerve disorder Asy diag inte Definition: A disorder characterized by Acoustic nerve disorder NOS Asy diag inte Definition: A disorder characterized by Akathisia Mild Mod Definition: A disorder characterized by Amnesia Mild Definition: A disorder characterized by Aphonia Definition: A disorder characterized by Aphonia Definition: A disorder characterized by Aphonia Definition: A disorder characterized by Aphonia	symptomatic; clinical or agnostic observations only; tervention not indicated by involvement of the accessor agnostic observations only; tervention not indicated by involvement of the acoustic observations only; tervention not indicated by involvement of the acoustic observations or increased of a country of the acoustic of the accessor of the acce	Moderate symptoms; limiting instrumental ADL y nerve (eleventh cranial nerve). Moderate symptoms; limiting instrumental ADL nerve (eighth cranial nerve). Moderate restlessness or increased motor activity; limiting instrumental ADL	care ADL Severe symptoms; limiting self care ADL Severe restlessness or increased motor activity; limiting	-	-
Definition: A disorder characterized by Acoustic nerve disorder NOS Asy diaginter Definition: A disorder characterized by Akathisia Milot Amnesia Milot Amnesia Milot Aphonia - Definition: A disorder characterized by Aphonia - Definition: A disord	agnostic observations only; tervention not indicated by involvement of the accessor symptomatic; clinical or agnostic observations only; tervention not indicated by involvement of the acoustic of ld restlessness or increased otor activity by an uncomfortable feeling of i	instrumental ADL y nerve (eleventh cranial nerve). Moderate symptoms; limiting instrumental ADL nerve (eighth cranial nerve). Moderate restlessness or increased motor activity; limiting instrumental ADL	care ADL Severe symptoms; limiting self care ADL Severe restlessness or increased motor activity; limiting	-	-
Acoustic nerve disorder NOS diaginte Definition: A disorder characterized b Akathisia Milk Molecular Milk Molecular Milk Molecular Milk Molecular Milk Molecular Milk Molecular Milk Molecular Milk Definition: A disorder characterized b Aphonia - Definition: A disorder characterized b	symptomatic; clinical or agnostic observations only; ervention not indicated by involvement of the acoustic old restlessness or increased otor activity by an uncomfortable feeling of ild; transient memory loss	Moderate symptoms; limiting instrumental ADL nerve (eighth cranial nerve). Moderate restlessness or increased motor activity; limiting instrumental ADL	Severe restlessness or increased motor activity; limiting	-	-
Definition: A disorder characterized by Akathisia Mild Mild Mild Mild Mild Mild Mild Mild	agnostic observations only; ervention not indicated by involvement of the acoustic of the acou	instrumental ADL nerve (eighth cranial nerve). Moderate restlessness or increased motor activity; limiting instrumental ADL	Severe restlessness or increased motor activity; limiting	-	-
Akathisia Milo Definition: A disorder characterized by Amnesia Milo Definition: A disorder characterized by Aphonia - Definition: A disorder characterized by	ld restlessness or increased otor activity by an uncomfortable feeling of i	Moderate restlessness or increased motor activity; limiting instrumental ADL	increased motor activity; limiting	-	
Definition: A disorder characterized by Amnesia Milo Definition: A disorder characterized by Aphonia - Definition: A disorder characterized by	otor activity by an uncomfortable feeling of i	increased motor activity; limiting instrumental ADL	increased motor activity; limiting	-	
Amnesia Mild Definition: A disorder characterized by Aphonia - Definition: A disorder characterized by Amazen and Amazen and Amazen and Amazen and Amazen and Amazen and Amazen and Amazen and Amazen and Amazen and Amazen	ld; transient memory loss	inner restlessness and inability to	self care ADL		-
Definition: A disorder characterized by Aphonia - Definition: A disorder characterized by			stay still; this is a side effect of sor	me psychotropic drugs.	
Aphonia - Definition: A disorder characterized by	by systematic and extensive inc	Moderate; short term memory loss; limiting instrumental ADL	Severe; long term memory loss; limiting self care ADL	-	-
Definition: A disorder characterized by		ss of memory.	I		Τ
		-	Voicelessness; unable to speak	1	-
Arachnoiditis		-		i i	T
		Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by		•	· ·		
diag		Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; mechanical assistance indicated	-	-
Definition: A disorder characterized by	by lack of coordination of muscl	le movements resulting in the imp	airment or inability to perform volu	ntary activities.	
dia		Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by	by regional paresthesia of the b	orachial plexus, marked discomfor	t and muscle weakness, and limite	ed movement in the arm or hand.	
necrosis diag	symptomatic; clinical or agnostic observations only; ervention not indicated	Moderate symptoms; corticosteroids indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by	by a necrotic process occurring	in the brain and/or spinal cord.	1	_	
Pos hea	adache; postural care dicated	Post-craniotomy: moderate symptoms; medical intervention indicated; Post-lumbar puncture: persistent moderate symptoms; blood patch indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by	by loss of cerebrospinal fluid int	to the surrounding tissues.	1	_	
inte per edu	erfering with work/school/life erformance; specialized ducational services/devices et indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	-	-
Definition: A disorder characterized by	by a conspicuous change in coo	gnitive function.	1		
· ·	vel of concentration	Moderate impairment in attention or decreased level of concentration; limiting instrumental ADL	Severe impairment in attention or decreased level of concentration; limiting self care ADL	-	-

Grade							
Adverse Event	1	2	3	4	5		
Adverse Event	Decreased level of alertness	Sedation; slow response to	Difficult to arouse				
Depressed level of consciousness	Decreased level of alerthess	stimuli; limiting instrumental ADL	Difficult to arouse	Life-threatening consequences	Death		
Definition: A disorder characte	rized by a decrease in ability to perc	eive and respond.	'	'			
Dizziness	Mild unsteadiness or sensation	Moderate unsteadiness or	Severe unsteadiness or	-	-		
	of movement	sensation of movement; limiting instrumental ADL	sensation of movement; limiting self care ADL				
Definition: A disorder characte	rized by a disturbing sensation of lig	htheadedness, unsteadiness, gidd	liness, spinning or rocking.				
Dysarthria	Mild slurred speech	Moderate impairment of articulation or slurred speech	Severe impairment of articulation or slurred speech	-	-		
Definition: A disorder characte	rized by slow and slurred speech re	sulting from an inability to coordina	ate the muscles used in speech.				
Dysesthesia	Mild sensory alteration	Moderate sensory alteration; limiting instrumental ADL	Severe sensory alteration; limiting self care ADL	-	-		
Definition: A disorder characte	rized by distortion of sensory percep	tion, resulting in an abnormal and	unpleasant sensation.	'			
Dysgeusia	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	-	-	-		
Definition: A disorder characte	ा rized by abnormal sensual experien	ı	। an be related to a decrease in the s	sense of smell.	ı		
Dysphasia	Awareness of receptive or expressive characteristics; not	Moderate receptive or expressive characteristics; impairing ability to communicate spontaneously	Severe receptive or expressive characteristics; impairing ability	-	-		
Definition: A disorder characte	rized by impairment of verbal comm	unication skills, often resulting fron	n brain damage.	ı			
Edema cerebral	-	-	-	Life-threatening consequences; urgent intervention indicated	-		
Definition: A disorder characte	rized by swelling due to an excessiv	e accumulation of fluid in the brain	l. T	T			
Encephalopathy	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characte	rized by a pathologic process involving	ing the brain.	1	Г	1		
Extrapyramidal disorder	Mild involuntary movements	Moderate involuntary movements; limiting instrumental ADL	Severe involuntary movements or torticollis; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characte	rized by abnormal, repetitive, involu	ntary muscle movements, frenzied	speech and extreme restlessness	S.			
Facial muscle weakness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-		
Definition: A disorder characte	rized by a reduction in the strength o	of the facial muscles.	1	<u> </u>			
Facial nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-		
Definition: A disorder characte	rized by involvement of the facial ne	rve (seventh cranial nerve).					
Glossopharyngeal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characte	rized by involvement of the glossoph	naryngeal nerve (ninth cranial nerv	e).				
Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-		
Definition: A disorder characte	rized by a sensation of marked disco	omfort in various parts of the head	, not confined to the area of distrib	ution of any nerve.			
Hydrocephalus	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; intervention not indicated	Severe symptoms or neurological deficit; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characte	rized by an abnormal increase of ce	· rebrospinal fluid in the ventricles o					
Hypersomnia	Mild increased need for sleep	Moderate increased need for sleep	Severe increased need for sleep	-	-		
Definition: A disorder aborests	rized by characterized by excessive		•	•	•		

	1	Nervous system dis	orders		
		I	Grade	I	1
Adverse Event	1	2	3	4	5
Hypoglossal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characteri	zed by involvement of the hypoglos	sal nerve (twelfth cranial nerve).			
Intracranial hemorrhage	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteri	zed by bleeding from the cranium.	,			
Ischemia cerebrovascular	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	-	-	-
Definition: A disorder characteri damage.	zed by a decrease or absence of bl	ood supply to the brain caused by	obstruction (thrombosis or embol	ism) of an artery resulting in neuro	logical
IVth nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characteri	zed by involvement of the trochlear		I	1	
Lethargy	Mild symptoms; reduced alertness and awareness	Moderate symptoms; limiting instrumental ADL	-	-	-
Definition: A disorder characteri	zed by a decrease in consciousnes	s characterized by mental and ph	ysical inertness.		
Leukoencephalopathy	Asymptomatic; small focal T2/FLAIR hyperintensities; involving periventricular white matter or <1/3 of susceptible areas of cerebrum +/- mild increase in subarachnoid space (SAS) and/or mild ventriculomegaly	Moderate symptoms; focal T2/FLAIR hyperintensities, involving periventricular white matter extending into centrum semiovale or involving 1/3 to 2/3 of susceptible areas of cerebrum +/- moderate increase in SAS and/or moderate ventriculomegaly	Severe symptoms; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving 2/3 or more of susceptible areas of cerebrum +/- moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Life-threatening consequences; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving most of susceptible areas of cerebrum +/- moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Death
Definition: A disorder characteri	zed by diffuse reactive astrocytosis	with multiple areas of necrotic foo	ci without inflammation.	T	
Memory impairment	Mild memory impairment	Moderate memory impairment; limiting instrumental ADL	Severe memory impairment; limiting self care ADL	-	-
Definition: A disorder characteri	zed by a deterioration in memory fu	inction.	1	1	
Meningismus	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteri	zed by neck stiffness, headache, a	nd photophobia resulting from irrita	ation of the cerebral meninges.		
Movements involuntary	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characteri	zed by uncontrolled and purposeles	ss movements.	1	1	
Myelitis	Asymptomatic; mild signs (e.g., Babinski's reflex or Lhermitte's sign)	Moderate weakness or sensory loss; limiting instrumental ADL	Severe weakness or sensory loss; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
	zed by inflammation involving the s	i i	T .	marked discomfort and incontiner	nce.
Neuralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
	zed by intense painful sensation ald				1
Nystagmus	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characteri	zed by involuntary movements of th	ne eyeballs. T	T	1	
Oculomotor nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characteri	zed by involvement of the oculomo	tor nerve (third cranial nerve).	T		
Olfactory nerve disorder	-	Moderate symptoms; limiting	Severe symptoms; limiting self	-	-

		Nervous system dis	orders		
		·	Grade		
Adverse Event	1	2	3	4	5
Paresthesia	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characteriz are experienced in the absence of		ensory neurons resulting in abnor	mal cutaneous sensations of tingli	ng, numbness, pressure, cold, and	warmth that
Peripheral motor neuropathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; assistive device indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by inflammation or degeneration	on of the peripheral motor nerves.			
Peripheral sensory neuropathy	Asymptomatic; loss of deep tendon reflexes or paresthesia	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
		on of the peripheral sensory nerve			
Phantom pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by marked discomfort related to		ed from or is not physically part of	the body.	
Presyncope	-	Present (e.g., near fainting)	-	-	-
Definition: A disorder characteriz	ed by an episode of lightheadedne	ess and dizziness which may prec	ede an episode of syncope.	T	I
Pyramidal tract syndrome	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
	ed by dysfunction of the corticospi nd a decrease in fine motor coord		l cord. Symptoms include an incre	ease in the muscle tone in the lowe	er extremities,
Radiculitis	Mild symptoms	Moderate symptoms; limiting instrumental ADL; medical intervention indicated	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz connecting nerve root.	ed by inflammation involving a ne	rve root. Patients experience mark	ed discomfort radiating along a ne	erve path because of spinal pressu	re on the
Recurrent laryngeal nerve palsy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	Severe symptoms; medical intervention indicated (e.g., thyroplasty, vocal cord injection)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by paralysis of the recurrent la	ryngeal nerve.			
Reversible posterior leukoencephalopathy syndrome	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; abnormal imaging studies; limiting instrumental ADL	Severe symptoms; very abnormal imaging studies; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
	-	=		findings of posterior leukoencepha s an acute or subacute reversible o	
Seizure	Brief partial seizure; no loss of consciousness	Brief generalized seizure	Multiple seizures despite medical intervention	Life-threatening; prolonged repetitive seizures	Death
Definition: A disorder characteriz	ed by a sudden, involuntary skele	tal muscular contractions of cereb	ral or brain stem origin.	T	
Sinus pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by marked discomfort in the fac	ce, between the eyes, or upper tee	eth originating from the sinuses.	1	ı
Somnolence	Mild but more than usual drowsiness or sleepiness	Moderate sedation; limiting instrumental ADL	Obtundation or stupor	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by characterized by excessive	sleepiness and drowsiness.	1	T	
Spasticity	Mild or slight increase in muscle tone	Moderate increase in muscle tone and increase in resistance through range of motion	Severe increase in muscle tone and increase in resistance through range of motion	Life-threatening; unable to move active or passive range of motion	Death
Definition: A disorder characteriz disturbances.	ed by increased involuntary musc			It results in gait, movement, and s	peech
Stroke	Asymptomatic or mild neurologic deficit; radiographic findings only	Moderate neurologic deficit	Severe neurologic deficit	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by a sudden loss of sensory fu	nction due to an intracranial vascu	lar event.		
Syncope Definition: A disorder characteriz	- ed by spontaneous loss of conscie	- busness caused by insufficient blo	Fainting; orthostatic collapse od supply to the brain.	-	-

		Nervous system dis	orders		
			Grade		
Adverse Event	1	2	3	4	5
Transient ischemic attacks	Mild neurologic deficit with or without imaging confirmation	Moderate neurologic deficit with or without imaging confirmation	-	-	-
Definition: A disorder characteriz	ed by a brief attack (less than 24 h	nours) of cerebral dysfunction of va	ascular origin, with no persistent n	eurological deficit.	
Tremor	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by the uncontrolled shaking mo	vement of the whole body or indiv	ridual parts.		
Trigeminal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by involvement of the trigemina	l nerve (fifth cranial nerve).			
Vagus nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by involvement of the vagus ne	rve (tenth cranial nerve).	•		
Vasovagal reaction	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz increase in the stimulation of the	ed by a sudden drop of the blood progressing vagus nerve.	oressure, bradycardia, and periph	eral vasodilation that may lead to	loss of consciousness. It results fr	om an
Nervous system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

	Pregna	ancy, puerperium and pe	rinatal conditions					
	Grade							
Adverse Event	1	2	3	4	5			
Fetal death	-	-	-	-	Fetal loss at any gestational age			
Definition: A disorder characterize	ed by death in utero; failure of the	product of conception to show evi	dence of respiration, heartbeat, or	definite movement of a voluntary	muscle after			
expulsion from the uterus, withou	t possibility of resuscitation.							
Fetal growth retardation	-	<10% percentile of weight for gestational age	<5% percentile of weight for gestational age	<1% percentile of weight for gestational age	-			
Definition: A disorder characterize	ed by inhibition of fetal growth resu	ulting in the inability of the fetus to	achieve its potential weight.					
Premature delivery	Delivery of a liveborn infant at >34 to 37 weeks gestation	Delivery of a liveborn infant at >28 to 34 weeks gestation	Delivery of a liveborn infant at 24 to 28 weeks gestation	Delivery of a liveborn infant at 24 weeks of gestation or less	-			
Definition: A disorder characterize gestation.	ed by delivery of a viable infant be	fore the normal end of gestation.	Typically, viability is achievable be	tween the twentieth and thirty-sev	enth week of			
Unintended pregnancy	-	-	Unintended pregnancy	-	-			
Definition: A disorder characterize	ed by an unexpected pregnancy a	t the time of conception.	•					
Pregnancy, puerperium and perinatal conditions - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate, local or noninvasive intervention indicated; limiting instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated;	Life-threatening consequences; urgent intervention indicated	Death			
			disabling; limiting self care ADL					

		Psychiatric disor	ders		
			Grade		
Adverse Event	1	2	3	4	5
Agitation	Mild mood alteration	Moderate mood alteration	Severe agitation; hospitalization not indicated	Life-threatening consequences; urgent intervention indicated	Death
	erized by a state of restlessness asso		irritability and tension.		
Anorgasmia	Inability to achieve orgasm not adversely affecting relationship	Inability to achieve orgasm adversely affecting relationship	-	-	-
	erized by an inability to achieve orgas				
Anxiety	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization not indicated	Life-threatening; hospitalization indicated	Death
Definition: A disorder characte stimulus.	erized by apprehension of danger and	d dread accompanied by restlessn	ess, tension, tachycardia, and dys	pnea unattached to a clearly iden	tifiable
Confusion	Mild disorientation	Moderate disorientation; limiting instrumental ADL	Severe disorientation; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	erized by a lack of clear and orderly the	nought and behavior.			
Delayed orgasm		Delay in achieving orgasm adversely affecting relationship	-	-	-
	erized by sexual dysfunction characte		T	I	I_
Delirium	Mild acute confusional state	Moderate and acute confusional state; limiting instrumental ADL	Severe and acute confusional state; limiting self care ADL; hospitalization indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder character reversible condition.	erized by the acute and sudden devel	opment of confusion, illusions, mo	ovement changes, inattentiveness,	agitation, and hallucinations. Usu	ally, it is a
Delusions	-	Moderate delusional symptoms	Severe delusional symptoms; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characte	erized by false personal beliefs held c	ontrary to reality, despite contradi	ctory evidence and common sense	e.	
Depression	Mild depressive symptoms	Moderate depressive symptoms; limiting instrumental ADL	Severe depressive symptoms; limiting self care ADL; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characte	erized by melancholic feelings of grief	or unhappiness.	'	'	•
Euphoria	Mild mood elevation	Moderate mood elevation	Severe mood elevation (e.g., hypomania)	-	-
Definition: A disorder characte	erized by an exaggerated feeling of w	ell-being which is disproportionate	to events and stimuli.		
Hallucinations	Mild hallucinations (e.g., perceptual distortions)	Moderate hallucinations	Severe hallucinations; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characte	erized by a false sensory perception i	n the absence of an external stimu	ulus.		
Insomnia	Mild difficulty falling asleep, staying asleep or waking up early	Moderate difficulty falling asleep, staying asleep or waking up early	Severe difficulty in falling asleep, staying asleep or waking up early	-	-
Definition: A disorder characte	erized by difficulty in falling asleep an	d/or remaining asleep.			
Libido decreased	Decrease in sexual interest not adversely affecting relationship	Decrease in sexual interest adversely affecting relationship	-	-	-
Definition: A disorder characte	erized by a decrease in sexual desire	T	1	T	1
Libido increased	Mild increase in sexual interest not adversely affecting relationship	Moderate increase in sexual interest adversely affecting relationship	Severe increase in sexual interest leading to dangerous behavior	-	-
Definition: A disorder characte	erized by an increase in sexual desire).			
Mania	Mild manic symptoms (e.g., elevated mood, rapid thoughts, rapid speech, decreased need for sleep)	Moderate manic symptoms (e.g., relationship and work difficulties; poor hygiene)	Severe manic symptoms (e.g., hypomania; major sexual or financial indiscretions); hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characte	erized by excitement of psychotic prop	oortions manifested by mental and	l physical hyperactivity, disorganiz	ation of behavior and elevation of	mood.
Personality change	Mild personality change	Moderate personality change	Severe personality change; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death

		Psychiatric disord	ders					
	Grade							
Adverse Event	1	2	3	4	5			
Definition: A disorder characterize	ed by a conspicuous change in a p	person's behavior and thinking.						
Psychosis	Mild psychotic symptoms	Moderate psychotic symptoms (e.g., disorganized speech; impaired reality testing)	Severe psychotic symptoms (e.g., paranoid; extreme disorganization); hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death			
Definition: A disorder characterize tumor.	ed by personality change, impaired	d functioning, and loss of touch wi	th reality. It may be a manifestatio	n of schizophrenia, bipolar disorde	er or brain			
Restlessness	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-			
Definition: A disorder characterize	ed by an inability to rest, relax or b	e still.						
Suicidal ideation	Increased thoughts of death but no wish to kill oneself	Suicidal ideation with no specific plan or intent	Specific plan to commit suicide without serious intent to die which may not require hospitalization	Specific plan to commit suicide with serious intent to die which requires hospitalization	-			
Definition: A disorder characterize	ed by thoughts of taking one's owr	n life.						
Suicide attempt	-	-	Suicide attempt or gesture without intent to die which may not require hospitalization	Suicide attempt with intent to die which requires hospitalization	Death			
Definition: A disorder characterize	ed by self-inflicted harm in an atter	mpt to end one's own life.						
Psychiatric disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; disabling; limiting self care ADL	Life-threatening consequences; hospitalization or urgent intervention indicated	Death			

Renal and urinary disorders							
			Grade				
Adverse Event	1	2	3	4	5		
Acute kidney injury Definition: A disorder character	Creatinine level increase of >0.3 mg/dL; creatinine 1.5 - 2.0 x above baseline ized by the acute loss of renal functions.	baseline	Creatinine >3 x baseline or >4.0 mg/dL; hospitalization indicated	Life-threatening consequences; dialysis indicated	Death		
causes (ureteral or bladder out		,		,,,			
Bladder perforation	-	Extraperitoneal perforation, indwelling catheter indicated	Intraperitoneal perforation; elective radiologic, endoscopic or operative intervention indicated	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death		
Definition: A disorder character	ized by a rupture in the bladder wall		1	<u> </u>	,		
Bladder spasm	Intervention not indicated	Antispasmodics indicated	Hospitalization indicated	-	-		
Definition: A disorder character	ized by a sudden and involuntary co	ontraction of the bladder wall.					
Chronic kidney disease	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <lln -="" 60<br="">ml/min/1.73 m2 or proteinuria 2+ present; urine protein/creatinine >0.5</lln>	eGFR or CrCl 59 - 30 ml/min/1.73 m2	eGFR or CrCl 29 - 15 ml/min/1.73 m2	eGFR or CrCl <15 ml/min/1.73 m2; dialysis or renal transplant indicated	Death		
Definition: A disorder character	ized by gradual and usually perman	ent loss of kidney function resulting	ng in renal failure.	-			
Cystitis noninfective	Microscopic hematuria; minimal increase in frequency, urgency, dysuria, or nocturia; new onset of incontinence	Moderate hematuria; moderate increase in frequency, urgency, dysuria, nocturia or incontinence; urinary catheter placement or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death		
Definition: A disorder character	ized by inflammation of the bladder	, which is not caused by an infectio	n of the urinary tract.	•	•		
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated; limiting self care ADL	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death		
Definition: A disorder character	ized by laboratory test results that ir	ndicate blood in the urine.					
Hemoglobinuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-		
Definition: A disorder character	ized by laboratory test results that in	ndicate the presence of free hemo	globin in the urine.				
Proteinuria	1+ proteinuria; urinary protein <1.0 g/24 hrs	Adults: 2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Pediatric: urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Adults: urinary protein >=3.5 g/24 hrs; Pediatric: urine P/C >1.9	-	-		
Definition: A disorder character	ized by laboratory test results that in	ndicate the presence of excessive	protein in the urine. It is predomin	antly albumin, but also globulin.			
Renal calculi	Asymptomatic or mild symptoms; occasional use of nonprescription analgesics indicated	Symptomatic; oral antiemetics indicated; around the clock nonprescription analgesics or any oral narcotic analgesics indicated	Hospitalization indicated; IV intervention (e.g., analgesics, antiemetics); elective endoscopic or radiologic intervention indicated	Life-threatening consequences; urgent radiologic, endoscopic or operative intervention indicated	Death		
Definition: A disorder character	ized by the formation of crystals in the	he pelvis of the kidney.					
Renal colic	Mild pain not interfering with activity; nonprescription medication indicated	Moderate pain; limiting instrumental ADL; prescription medication indicated	Hospitalization indicated; limiting self care ADL	-	-		

		Renal and urinary di	sorders		
			Grade		
Adverse Event	1	2	3	4	5
Renal hemorrhage	Mild symptoms; intervention not indicated	Analgesics and hematocrit monitoring indicated	Transfusion, radiation, or hospitalization indicated; elective radiologic, endoscopic or operative intervention indicated	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder character	ized by bleeding from the kidney.				
Urinary fistula	-	Noninvasive intervention indicated; urinary or suprapubic catheter placement indicated	Limiting self care ADL; elective radiologic, endoscopic or operative intervention indicated; permanent urinary diversion indicated	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder character	ized by an abnormal communication	between any part of the urinary s	system and another organ or anato	omic site.	
Urinary frequency	Present	Limiting instrumental ADL; medical management indicated	-	-	-
Definition: A disorder character	ized by urination at short intervals.	T	1	T	T
Urinary incontinence	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous; pads indicated; limiting instrumental ADL	Intervention indicated (e.g., clamp, collagen injections); operative intervention indicated; limiting self care ADL	-	-
Definition: A disorder character	ized by inability to control the flow o	f urine from the bladder.			
Urinary retention	Urinary, suprapubic or intermittent catheter placement not indicated; able to void with some residual	Placement of urinary, suprapubic or intermittent catheter placement indicated; medication indicated	Elective operative or radiologic intervention indicated; substantial loss of affected kidney function or mass	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
Definition: A disorder character	ized by accumulation of urine within	the bladder because of the inabil	ity to urinate.		
Urinary tract obstruction	Asymptomatic; clinical or diagnostic observations only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; urethral dilation, urinary or suprapubic catheter indicated	Symptomatic and altered organ function (e.g., hydronephrosis, or renal dysfunction); elective radiologic, endoscopic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder character	ized by blockage of the normal flow	of contents of the urinary tract.	T	T	1
Urinary tract pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder character	ized by a sensation of marked disco	omfort in the urinary tract.	1	T	
Urinary urgency	Present	Limiting instrumental ADL; medical management indicated	-	-	-
Definition: A disorder character	ized by a sudden compelling urge to	urinate.	,		
Urine discoloration	Present	-	-	-	-
Definition: A disorder character	ized by a change in the color of the	urine.			
Renal and urinary disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate, local or noninvasive intervention indicated; limiting instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

	Rep	productive system and b	reast disorders		
			Grade		
Adverse Event	1	2	3	4	5
Azoospermia	-	-	Absence of sperm in ejaculate	-	-
Definition: A disorder characte	erized by laboratory test results that ir	ndicate complete absence of speri	matozoa in the semen.		•
Breast atrophy	Minimal asymmetry; minimal	Moderate asymmetry; moderate	Asymmetry >1/3 of breast	-	-
	atrophy	atrophy	volume; severe atrophy		
Definition: A disorder characte	erized by underdevelopment of the br	east.	'	'	•
Breast pain	Mild pain	Moderate pain; limiting	Severe pain; limiting self care	-	_
,		instrumental ADL	ADL		
Definition: A disorder characte	erized by marked discomfort sensation	n in the breast region.	'	'	•
Dysmenorrhea	Mild symptoms; intervention not		Severe symptoms; limiting self	_	_
-,	indicated	instrumental ADL	care ADL		
Definition: A disorder characte	erized by abnormally painful abdomin	al cramps during menses.	!	!	'
Dyspareunia	Mild discomfort or pain	Moderate discomfort or pain	Severe discomfort or pain		
3y3parcuma	associated with vaginal	associated with vaginal	associated with vaginal		
	penetration; discomfort relieved	penetration; discomfort or pain	penetration; discomfort or pain		
	with use of vaginal lubricants or	partially relieved with use of	unrelieved by vaginal lubricants		
	estrogen	vaginal lubricants or estrogen	or estrogen		
Definition: A disorder characte	erized by painful or difficult coitus.				_
Ejaculation disorder	Diminished ejaculation	Anejaculation or retrograde	-	-	-
		ejaculation			
Definition: A disorder characte	erized by problems related to ejaculat	, ion. This category includes prema	ture, delayed, retrograde and pair	ful ejaculation.	•
Erectile dysfunction	Decrease in erectile function	Decrease in erectile function	Decrease in erectile function	-	_
,	(frequency or rigidity of	(frequency/rigidity of erections),	(frequency/rigidity of erections)		
	erections) but intervention not	erectile intervention indicated,	but erectile intervention not		
	indicated (e.g., medication or	(e.g., medication or mechanical	helpful (e.g., medication or		
	use of mechanical device,	devices such as penile pump)	mechanical devices such as		
	penile pump)		penile pump); placement of a		
			permanent penile prosthesis		
			indicated (not previously present)		
Definition: A disorder character	rized by the persistent or recurrent in	 		I	1
	erized by the persistent or recurrent in				
Fallopian tube obstruction	Diagnostic observations only;	Mild symptoms; elective	Severe symptoms; elective	=	-
	intervention not indicated	intervention indicated	operative intervention indicated		l
Definition: A disorder characte	erized by blockage of the normal flow	of the contents in the fallopian tub	oe.		
Fallopian tube stenosis	Asymptomatic clinical or	Symptomatic and intervention	Severe symptoms; elective	Life-threatening consequences;	Death
	diagnostic observations only;	not indicated	operative intervention indicated	urgent operative intervention	
	intervention not indicated			indicated (e.g., organ resection)	I
	erized by a narrowing of the fallopian				1
Female genital tract fistula	Asymptomatic clinical or	Symptomatic and intervention	Severe symptoms; elective	Life-threatening consequences;	Death
	diagnostic observations only;	not indicated	operative intervention indicated	urgent intervention indicated	
	intervention not indicated				I
Definition: A disorder characte	erized by an abnormal communication	n between a female reproductive s	system organ and another organ o	r anatomic site.	
Feminization acquired	Mild symptoms; intervention not	1	-	-	-
	indicated	intervention indicated			
Definition: A disorder characte	erized by the development of seconda	ary female sex characteristics in m	nales due to extrinsic factors.	1	
Genital edema	Mild swelling or obscuration of	Readily apparent obscuration of	Lymphorrhea; gross deviation	-	-
	anatomic architecture on close	anatomic architecture;	from normal anatomic contour;		
	inspection	obliteration of skin folds; readily	limiting self care ADL		
		apparent deviation from normal			
Definition, A dis	primad by availing due to an arm	anatomic contour		I	I
	erized by swelling due to an excessive				
Gynecomastia	Asymptomatic breast	Symptomatic (e.g., pain or	Severe symptoms; elective	-	-
	enlargement	psychosocial impact)	operative intervention indicated		I
Definition: A disorder characte	erized by excessive development of the	ne breasts in males.	1	1	_
Hematosalpinx	Minimal bleeding identified on	Moderate bleeding; medical	Severe bleeding; transfusion	Life-threatening consequences;	Death
	imaging study or laparoscopy;	intervention indicated	indicated; radiologic or	urgent operative intervention	
	intervention not indicated		endoscopic intervention	indicated	
	1	l .	indicated	1	1

	Rep	productive system and bu	east disorders					
	Grade							
Adverse Event	1	2	3	4	5			
Definition: A disorder characteri	ized by the presence of blood in a fa	allopian tube.						
rregular menstruation	Intermittent menses with skipped menses for no more than 1 to 3 months	Intermittent menses with skipped menses for more than 4 to 6 months	Persistent amenorrhea for more than 6 months	-	-			
Definition: A disorder characteri	ized by irregular cycle or duration of	menses.	Γ	Γ	1			
actation disorder	Mild changes in lactation, not significantly affecting production or expression of breast milk	Changes in lactation, significantly affecting breast production or expression of breast milk	-	-	-			
Definition: A disorder characteri	ized by disturbances of milk secretion	on. It is not necessarily related to p	pregnancy that is observed in fema	ales and can be observed in males	S.			
Menorrhagia	Mild; iron supplements indicated	Moderate symptoms; medical intervention indicated (e.g., hormones)	Severe; transfusion indicated; surgical intervention indicated (e.g., hysterectomy)	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteri	ized by abnormally heavy vaginal bl	eeding during menses.						
Nipple deformity	Asymptomatic; asymmetry with slight retraction and/or thickening of the nipple areolar complex	Symptomatic; asymmetry of nipple areolar complex with moderate retraction and/or thickening of the nipple areolar complex	-	-	-			
Definition: A disorder characteri	zed by a malformation of the nipple	•						
Oligospermia	Sperm concentration >48 million/mL or motility >68%	Sperm concentration 13 - 48 million/mL or motility 32 - 68%	Sperm concentration <13 million/mL or motility <32%	-	-			
Definition: A disorder characteri	ized by a decrease in the number of	spermatozoa in the semen.						
Ovarian hemorrhage	Minimal bleeding identified on imaging study or laproscopy; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characteri	ized by bleeding from the ovary.	1	•	'				
Ovarian rupture	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteri	ized by tearing or disruption of the c	varian tissue.	, .		'			
Ovulation pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characteri ovarian follicle.	ized by marked discomfort sensatio	n in one side of the abdomen betw	veen menstrual cycles, around the	time of the discharge of the ovum	from the			
Pelvic floor muscle weakness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic, not interfering with bladder, bowel, or vaginal function; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteri	zed by a reduction in the strength o	f the muscles of the pelvic floor.						
elvic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characteri	ized by marked discomfort sensatio	n in the pelvis.	I	I	1			
Penile pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
	ized by marked discomfort sensatio				1			
erineal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characteri	ized by a sensation of marked disco	mfort in the area between the ger	T	Т				
Premature menopause	-	-	Present	-	-			
Definition: A disorder characteri	zed by ovarian failure before the ag	e of 40. Symptoms include hot fla	shes, night sweats, mood swings	and a decrease in sex drive.				
Prostatic hemorrhage	Minimal bleeding identified on imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			

	Rep	productive system and be	reast disorders		
			Grade		
Adverse Event	1	2	3	4	5
Definition: A disorder characteriz	red by bleeding from the prostate of	pland.	1		
Prostatic obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characteriz stream, and incomplete emptyin	zed by compression of the urethra g of the bladder).	secondary to enlargement of the p	prostate gland. This results in voidi	ng difficulties (straining to void, sl	ow urine
Prostatic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by a sensation of marked disco	omfort in the prostate gland.			
Scrotal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by marked discomfort sensatio	n in the scrotal area.			
Spermatic cord hemorrhage	Minimal bleeding identified on imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteriz	ed by bleeding from the spermatic	cord.			
Spermatic cord obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characteriz	ed by blockage of the normal flow	of the contents of the spermatic c	ord.		
Festicular disorder	Asymptomatic; clinical or diagnostic observations only;	Symptomatic but not interfering with urination or sexual	Severe symptoms; interfering with urination or sexual function;	Life-threatening consequences; urgent intervention indicated	Death
	intervention not indicated	activities; intervention not indicated; limiting instrumental ADL	limiting self care ADL; intervention indicated		
Definition: A disorder characteriz	ed by involvement of the testis.	ı	!		'
Testicular hemorrhage	Minimal bleeding identified on imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteriz	red by bleeding from the testis.	1	1		
「esticular pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by a sensation of marked disco	omfort in the testis.			
Jterine fistula	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by an abnormal communication	n between the uterus and another	organ or anatomic site.		'
Jterine hemorrhage	Minimal bleeding identified on imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characteriz	red by bleeding from the uterus.				
Iterine obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characteriz	zed by blockage of the uterine outle	et.			
Iterine pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	red by a sensation of marked disco	omfort in the uterus.			
/aginal discharge	Mild vaginal discharge (greater than baseline for patient)	Moderate to heavy vaginal discharge; use of perineal pad or tampon indicated	-	-	-
Definition: A disorder characteriz	ed by vaginal secretions. Mucus p		discharged from the vagina natura	lly, especially during the childbea	ring years.
/aginal dryness	Mild vaginal dryness not interfering with sexual function	Moderate vaginal dryness interfering with sexual function	Severe vaginal dryness resulting in dyspareunia or severe discomfort	-	-
Definition: A disorder characteriz	l red by an uncomfortable feeling of	or causing frequent discomfort itching and burning in the vagina.	Joseph discombit	I	1

	Rep	productive system and b	reast disorders		
			Grade		
Adverse Event	1	2	3	4	5
Vaginal fistula	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by an abnormal communication	between the vagina and another	organ or anatomic site.		
Vaginal hemorrhage	Minimal bleeding identified on clinical exam or imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterize	ed by bleeding from the vagina.				
Vaginal inflammation	Mild discomfort or pain, edema, or redness	Moderate discomfort or pain, edema, or redness; limiting instrumental ADL	Severe discomfort or pain, edema, or redness; limiting self care ADL; small areas of mucosal ulceration	Widespread areas of mucosal ulceration; life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by inflammation involving the v	agina. Symptoms may include red	lness, edema, marked discomfort	and an increase in vaginal dischar	ge.
Vaginal obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterize	ed by blockage of vaginal canal.		1	1	
Vaginal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterize	ed by a sensation of marked disco	mfort in the vagina.			
Vaginal perforation	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterize	ed by a rupture in the vaginal wall.				•
Vaginal stricture	Asymptomatic; mild vaginal shortening or narrowing	Vaginal narrowing and/or shortening not interfering with physical examination	Vaginal narrowing and/or shortening interfering with the use of tampons, sexual activity or physical examination	-	Death
Definition: A disorder characterize	ed by a narrowing of the vaginal ca	anal.			
Vaginismus	Mild discomfort or pain associated with vaginal spasm/tightening; no impact upon sexual function or physical examination	Moderate discomfort or pain associated with vaginal spasm/tightening; disruption in sexual function and physical examination	Severe discomfort or pain associated with vaginal spasm/tightening; unable to tolerate vaginal penetration or physical examination	-	-
Definition: A disorder characterize intercourse.	ed by involuntary spasms of the pe	elvic floor muscles, resulting in pa	thologic tightness of the vaginal w	all during penetration such as duri	ng sexual
Reproductive system and breast disorders - Other, specify		Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

	Respi	ratory, thoracic and med	iastinal disorders					
	Grade							
Adverse Event	1	2	3	4	5			
Adult respiratory distress syndrome	-	-	Present with radiologic findings; intubation not indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death			
Definition: A disorder characteri surgery.	zed by progressive and life-threater	ning pulmonary distress in the abs	ence of an underlying pulmonary	condition, usually following major t	rauma or			
Allergic rhinitis	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-			
	zed by an inflammation of the nasa s of the sinuses, eyes, middle ear, a	•	•	•	ay also			
Apnea	-	-	Present; medical intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death			
Definition: A disorder characteri	zed by cessation of breathing.	I	1	T				
Aspiration	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Altered eating habits; coughing or choking episodes after eating or swallowing; medical intervention indicated (e.g., suction or oxygen)	Dyspnea and pneumonia symptoms (e.g., aspiration pneumonia); hospitalization indicated; unable to aliment orally	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death			
Definition: A disorder characteri	zed by inhalation of solids or liquids	s into the lungs.	1	<u> </u>				
Atelectasis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., dyspnea, cough); medical intervention indicated (e.g., chest physiotherapy, suctioning); bronchoscopic suctioning	Oxygen indicated; hospitalization or elective operative intervention indicated (e.g., stent, laser)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death			
Definition: A disorder characteri	zed by the collapse of part or the e	ntire lung.		T	1			
Bronchial fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical management indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death			
Definition: A disorder characteri	zed by an abnormal communication	between the bronchus and anoth	ner organ or anatomic site.	·				
Bronchial obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., mild wheezing); endoscopic evaluation indicated; radiographic evidence of atelectasis/lobar collapse; medical management indicated (e.g., steroids, bronchodilators)	Shortness of breath with stridor; endoscopic intervention indicated (e.g., laser, stent placement)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death			
Definition: A disorder characteri	zed by blockage of a bronchus pas	sage, most often by bronchial sec	retions and exudates.					
Bronchial stricture	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., rhonchi or wheezing) but without respiratory distress; medical intervention indicated (e.g., steroids, bronchodilators)	Shortness of breath with stridor; endoscopic intervention indicated (e.g., laser, stent placement)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death			
	zed by a narrowing of the bronchial			leg at the second	.			
Bronchopleural fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death			
Definition: A disorder characteri	zed by an abnormal communication	between a bronchus and the plei	ural cavity.	I				
Bronchopulmonary hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g.,	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention	Death			

	1100p	ratory, thoracic and med			
			Grade	1	_
Adverse Event	1	2	3	4	5
Bronchospasm	Mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Limiting self care ADL; oxygen saturation decreased	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder charact	terized by a sudden contraction of the	smooth muscles of the bronchial	wall.	1	1
Chylothorax	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thoracentesis or tube drainage indicated	Severe symptoms; elective operative intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder charact	terized by milky pleural effusion (abnor	rmal collection of fluid) resulting fr	om accumulation of lymph fluid in	the pleural cavity.	
Cough	Mild symptoms; nonprescription intervention indicated	Moderate symptoms, medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder charact by a distinctive sound.	terized by sudden, often repetitive, spa	asmodic contraction of the thoraci	c cavity, resulting in violent release	e of air from the lungs and usually a	accompar
Dyspnea	Shortness of breath with moderate exertion	Shortness of breath with minimal exertion; limiting instrumental ADL	Shortness of breath at rest; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder charact	terized by an uncomfortable sensation	of difficulty breathing.			
Epistaxis	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated (e.g., nasal packing, cauterization; topical vasoconstrictors)	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder charact	terized by bleeding from the nose.				
Hiccups	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe symptoms; interfering with sleep; limiting self care ADL	-	-
Definition: A disorder charact	terized by repeated gulp sounds that re	esult from an involuntary opening	and closing of the glottis. This is a	ttributed to a spasm of the diaphra	igm.
Hoarseness	Mild or intermittent voice change; fully understandable; self-resolves	Moderate or persistent voice changes; may require occasional repetition but understandable on telephone; medical evaluation indicated	Severe voice changes including predominantly whispered speech	-	-
Definition: A disorder charact	erized by harsh and raspy voice arisin	g from or spreading to the larynx.			
Hypoxia	erized by a decrease in the level of ox	Decreased oxygen saturation with exercise (e.g., pulse oximeter <88%); intermittent supplemental oxygen	Decreased oxygen saturation at rest (e.g., pulse oximeter <88% or PaO2 <=55 mm Hg)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Laryngeal edema	Asymptomatic; clinical or	Symptomatic; medical	Stridor; respiratory distress;	Life-threatening airway	Death
earyngour odollid	diagnostic observations only; intervention not indicated	intervention indicated (e.g., dexamethasone, epinephrine, antihistamines)	hospitalization indicated	compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Boun
	erized by swelling due to an excessive			Ī	I_
Laryngeal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical management indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention indicated (e.g., thoracoplasty, chronic open drainage or multiple thoracotomies)	Death
Definition: A disorder charact	erized by an abnormal communication	between the larynx and another	organ or anatomic site.		
Laryngeal hemorrhage	Mild cough or trace hemoptysis; laryngoscopic findings	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder abovest	erized by bleeding from the larynx.				
Delinition. A disorder charact					

	Respi	ratory, thoracic and med	lastinal disorders		
			Grade		
Adverse Event	1	2	3	4	5
Laryngeal mucositis	Endoscopic findings only; mild discomfort with normal intake	Moderate discomfort; altered oral intake	Severe pain; severely altered eating/swallowing; medical intervention indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characteri	zed by an inflammation involving th	e mucous membrane of the laryn	(.	İ	
Laryngeal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids); limiting instrumental ADL	Limiting self care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteri	zed by blockage of the laryngeal ai	rway.			
Laryngeal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Limiting self care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening consequences; urgent intervention indicated	Death
	zed by a narrowing of the laryngea		T		I
Laryngopharyngeal dysesthesia	a Mild symptoms; no anxiety; intervention not indicated	Moderate symptoms; mild anxiety, but no dyspnea; short duration of observation and or anxiolytic indicated; limiting instrumental ADL	Severe symptoms; dyspnea and swallowing difficulty; limiting self care ADL	Life-threatening consequences	Death
Definition: A disorder characteri	zed by an uncomfortable persistent	sensation in the area of the laryn	gopharynx.		
Laryngospasm	-	Transient episode; intervention not indicated	Recurrent episodes; noninvasive intervention indicated (e.g., breathing technique, pressure point massage)	Persistent or severe episodes associated with syncope; urgent intervention indicated (e.g., fiberoptic laryngoscopy, intubation, botox injection)	Death
Definition: A disorder characteri	zed by paroxysmal spasmodic mus	cular contraction of the vocal cord			'
Mediastinal hemorrhage	Radiologic evidence only; minimal symptoms; intervention not indicated	Moderate symptoms; medical	Transfusion, radiologic, endoscopic, or elective operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteri	zed by bleeding from the mediastin	um.	1 '	l	1
Nasal congestion	Mild symptoms; intervention not indicated		Associated with bloody nasal discharge or epistaxis	-	-
	zed by obstruction of the nasal pas	1			ı
Pharyngeal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteri	zed by an abnormal communication	between the pharynx and another	er organ or anatomic site.	<u> </u>	
Pharyngeal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characteri	zed by bleeding from the pharynx.	T			1
Pharyngeal mucositis	Endoscopic findings only; minimal symptoms with normal oral intake; mild pain but analgesics not indicated	Moderate pain and analgesics indicated; altered oral intake; limiting instrumental ADL	Severe pain; unable to adequately aliment or hydrate orally; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteri	zed by an inflammation involving th	e mucous membrane of the phary	nx.		
Pharyngeal necrosis	-	-	Inability to aliment adequately by GI tract; tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death

	Respir	ratory, thoracic and med	astinal disorders			
			Grade			
Adverse Event	1	2	3	4	5	
Definition: A disorder character	rized by a necrotic process occurring	in the pharynx.	1			
Pharyngeal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids); limiting instrumental ADL	Limiting self care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death	
Definition: A disorder character	rized by a narrowing of the pharynge	al airway.	,	'	•	
Pharyngolaryngeal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-	
Definition: A disorder character	rized by marked discomfort sensation	n in the pharyngolaryngeal region.	<u> </u>			
Pleural effusion	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; intervention indicated (e.g., diuretics or limited therapeutic thoracentesis)	Symptomatic with respiratory distress and hypoxia; surgical intervention including chest tube or pleurodesis indicated	indicated	Death	
Definition: A disorder character	rized by an increase in amounts of flo	uid within the pleural cavity. Symp	toms include shortness of breath,	cough and marked chest discomfo	ort.	
Pleural hemorrhage	Asymptomatic; mild hemorrhage confirmed by thoracentesis	Symptomatic or associated with pneumothorax; chest tube drainage indicated	>1000 ml of blood evacuated; persistent bleeding (150-200 ml/hr for 2 - 4 hr); persistent transfusion indicated; elective operative intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death	
Definition: A disorder character	rized by bleeding from the pleural ca	vity.	•	•	•	
Pleuritic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-	
Definition: A disorder character	rized by marked discomfort sensation	n in the pleura.	<u> </u>	T		
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death	
	rized by inflammation focally or diffus				I	
Pneumothorax	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; intervention indicated (e.g., tube placement without sclerosis)	Sclerosis and/or operative intervention indicated; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder character	rized by abnormal presence of air in	the pleural cavity resulting in the	collapse of the lung.			
Postnasal drip	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-	
Definition: A disorder character	rized by excessive mucous secretion	in the back of the nasal cavity or	throat, causing sore throat and/or	coughing.		
Productive cough		Moderate sputum production; limiting instrumental ADL	Persistent or copious production of sputum; limiting self care ADL	-	-	
	rized by expectorated secretions upo		Cayora dyannaa ar dyannaa at	Life threatening requireten.	Dooth	
Pulmonary edema	Radiologic findings only; minimal dyspnea on exertion	Moderate dyspnea on exertion; medical intervention indicated; limiting instrumental ADL	Severe dyspnea or dyspnea at rest; oxygen indicated; limiting self care ADL	Life-threatening respiratory compromise; urgent intervention or intubation with ventilatory support indicated	Death	
Definition: A disorder character	rized by accumulation of fluid in the I	ung tissues that causes a disturba	nce of the gas exchange that may	lead to respiratory failure.		
Pulmonary fibrosis	Mild hypoxemia; radiologic pulmonary fibrosis <25% of lung volume	Moderate hypoxemia; evidence of pulmonary hypertension; radiographic pulmonary fibrosis 25 - 50%	Severe hypoxemia; evidence of right-sided heart failure; radiographic pulmonary fibrosis >50 - 75%	Life-threatening consequences (e.g., hemodynamic/pulmonary complications); intubation with ventilatory support indicated; radiographic pulmonary fibrosis >75% with severe honeycombing	Death	
Definition: A disorder character	rized by the replacement of the lung	tissue by connective tissue, leadir	g to progressive dyspnea, respira	tory failure or right heart failure.		
Pulmonary fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical management indicated; limiting instrumental ADL	Limiting self care ADL; endoscopic stenting or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death	

	Respi	ratory, thoracic and med	iastinal disorders		
			Grade	1	1
Adverse Event	1	2	3	4	5
Definition: A disorder characteriz	red by an abnormal communication	between the lung and another or	gan or anatomic site.	1	
Pulmonary hypertension	Minimal dyspnea; findings on physical exam or other evaluation	Moderate dyspnea, cough; requiring evaluation by cardiac catheterization and medical intervention	Severe symptoms, associated with hypoxemia, right heart failure; oxygen indicated	Life-threatening airway consequences; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characteriz	ed by an increase in pressure with	in the pulmonary circulation due to	o lung or heart disorder.		
Respiratory failure	-	-	-	Life-threatening consequences; urgent intervention, intubation, or ventilatory support indicated	Death
Definition: A disorder characteriz with an increase in arterial levels	red by impaired gas exchange by t s of carbon dioxide.	he respiratory system resulting in	hypoxemia and a decrease in oxy	genation of the tissues that may be	e associate
Retinoic acid syndrome	Fluid retention; <3 kg of weight gain; intervention with fluid restriction and/or diuretics indicated	Moderate signs or symptoms; steroids indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; ventilatory support indicated	Death
Definition: A disorder characteriz	zed by weight gain, dyspnea, pleur	al and pericardial effusions, leukoo	cytosis and/or renal failure original	lly described in patients treated wit	h all-trans
Sinus disorder	Asymptomatic mucosal crusting; blood-tinged secretions	Symptomatic stenosis or edema/narrowing interfering with airflow; limiting instrumental ADL	Stenosis with significant nasal obstruction; limiting self care ADL	Necrosis of soft tissue or bone; urgent operative intervention indicated	Death
Definition: A disorder characteriz	red by involvement of the paranasa	al sinuses.	•		
Sleep apnea	Snoring and nocturnal sleep arousal without apneic periods	Moderate apnea and oxygen desaturation; excessive daytime sleepiness; medical evaluation indicated; limiting instrumental ADL	Oxygen desaturation; associated with hypertension; medical intervention indicated; limiting self care ADL	Cardiovascular or neuropsychiatric symptoms; urgent operative intervention indicated	Death
Definition: A disorder characteriz	ed by cessation of breathing for sh	nort periods during sleep.			
Sneezing	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characteriz	ed by the involuntary expulsion of	air from the nose.	'	'	
Sore throat	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL; limiting ability to swallow	-	-
Definition: A disorder characteriz	red by of marked discomfort in the	throat	'	•	•
Stridor	-	-	Respiratory distress limiting self care ADL; medical intervention indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characteriz	red by a high pitched breathing sou	und due to laryngeal or upper airw	ay obstruction.		
Tracheal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention indicated (e.g., thoracoplasty, chronic open drainage or multiple thoracotomies)	Death
Definition: A disorder characteriz	ed by an abnormal communication	between the trachea and another	r organ or anatomic site.		
Tracheal mucositis	Endoscopic findings only; minimal hemoptysis, pain, or respiratory symptoms	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe pain; hemorrhage or respiratory symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
	ted by an inflammation involving th			Ī	I_
Tracheal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Stridor or respiratory distress limiting self care ADL; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
	red by a narrowing of the trachea.	1	1	•	•

	Respi	ratory, thoracic and med	iastinal disorders				
	Grade						
Adverse Event	1	2	3	4	5		
Voice alteration	Mild or intermittent change from normal voice	Moderate or persistent change from normal voice; still understandable	Severe voice changes including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; may require assistive technology	-	-		
Definition: A disorder characteriz	ed by a change in the sound and/o	or speed of the voice.					
Wheezing	Detectable airway noise with minimal symptoms	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe respiratory symptoms limiting self care ADL; oxygen therapy or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characteriz	ed by a high-pitched, whistling sou	ind during breathing. It results from	n the narrowing or obstruction of t	he respiratory airways.			
Respiratory, thoracic and mediastinal disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death		

			Skin and subcutaneous tissue disorders							
Grade										
Adverse Event	1	2	3	4	5					
Alopecia	Hair loss of <50% of normal for that individual that is not obvious from a distance but only on close inspection; a different hair style may be required to	Hair loss of >=50% normal for that individual that is readily apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss;	-	-	-					
	cover the hair loss but it does not require a wig or hair piece to camouflage									
Definition: A disorder character	ized by a decrease in density of hair	· · compared to normal for a given i	ndividual at a given age and body	location.	,					
Body odor	Mild odor; physician intervention not indicated; self care interventions	Pronounced odor; psychosocial impact; patient seeks medical intervention	-	-	-					
Definition: A disorder character	ized by an abnormal body smell res	ulting from the growth of bacteria	on the body.		1					
Bullous dermatitis	Asymptomatic; blisters covering <10% BSA	Blisters covering 10 - 30% BSA; painful blisters; limiting instrumental ADL	Blisters covering >30% BSA; limiting self care ADL	Blisters covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death					
Definition: A disorder character	ized by inflammation of the skin cha	racterized by the presence of bull	ae which are filled with fluid.	T						
Ory skin	Covering <10% BSA and no associated erythema or pruritus	Covering 10 - 30% BSA and associated with erythema or pruritus; limiting instrumental ADL	Covering >30% BSA and associated with pruritus; limiting self care ADL	-	-					
Definition: A disorder character	ized by flaky and dull skin; the pores	are generally fine, the texture is	a papery thin texture.		_					
Erythema multiforme	Target lesions covering <10% BSA and not associated with skin tenderness	Target lesions covering 10 - 30% BSA and associated with skin tenderness	Target lesions covering >30% BSA and associated with oral or genital erosions	Target lesions covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death					
Definition: A disorder character	ized by target lesions (a pink-red rin	g around a pale center).	<u> </u>	<u> </u>						
Erythroderma	-	Erythema covering >90% BSA without associated symptoms; limiting instrumental ADL	Erythema covering >90% BSA with associated symptoms (e.g., pruritus or tenderness); limiting self care ADL	Erythema covering >90% BSA with associated fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death					
Definition: A disorder character	ized by generalized inflammatory er	ythema and exfoliation. The inflan	nmatory process involves > 90% o	f the body surface area.	_					
Fat atrophy	Covering <10% BSA and asymptomatic	Covering 10 - 30% BSA and associated with erythema or tenderness; limiting instrumental ADL	Covering >30% BSA; associated with erythema or tenderness; limiting self-care ADL	-	-					
	ized by shrinking of adipose tissue.				1					
Hirsutism	In women, increase in length, thickness or density of hair in a male distribution that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair	In women, increase in length, thickness or density of hair in a male distribution that requires daily shaving or consistent destructive means of hair removal to camouflage; associated with psychosocial impact	-	-	-					
Definition: A disorder character	ized by the presence of excess hair	growth in women in anatomic site	s where growth is considered to b	e a secondary male characteristic	and unde					
androgen control (beard, mous	* *									
Hyperhidrosis	Limited to one site (palms, soles, or axillae); self care interventions	Involving >1 site; patient seeks medical intervention; associated with psychosocial impact	Generalized involving sites other than palms, soles, or axillae; associated with electrolyte/hemodynamic imbalance	-	-					

	SK	in and subcutaneous tis	sue disorders		
		I	Grade		
Adverse Event	1	2	3	4	5
Hypertrichosis	Increase in length, thickness or density of hair that the patient is either able to camouflage by periodic shaving or removal of hairs or is not concerned	Increase in length, thickness or density of hair at least on the usual exposed areas of the body [face (not limited to beard/moustache area)	-	-	-
	enough about the overgrowth to use any form of hair removal	plus/minus arms] that requires frequent shaving or use of destructive means of hair removal to camouflage; associated with psychosocial			
D 5 ''' A 1''		impact			
Definition: A disorder characteri Hypohidrosis	zed by hair density or length beyon	Symptomatic; limiting instrumental ADL	Increase in body temperature;	Heat stroke	Death
Definition: A disorder characteri	zed by reduced sweating.	1	,	'	•
Lipohypertrophy	Asymptomatic and covering <10% BSA	Covering 10 - 30% BSA and associated tenderness; limiting instrumental ADL	Covering >30% BSA and associated tenderness and narcotics or NSAIDs indicated; lipohypertrophy; limiting self care ADL	-	-
Definition: A disorder characteri	zed by hypertrophy of the subcutan	eous adipose tissue at the site of	multiple subcutaneous injections of	of insulin.	,
Nail discoloration	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characteri	zed by a change in the color of the	nail plate.	T	T	1
Nail loss	Asymptomatic separation of the nail bed from the nail plate or nail loss	Symptomatic separation of the nail bed from the nail plate or nail loss; limiting instrumental ADL	-	-	-
Definition: A disorder characteri	zed by loss of all or a portion of the	nail.		•	•
Nail ridging	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characteri	zed by vertical or horizontal ridges	on the nails.	'	'	'
Pain of skin	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteri	zed by marked discomfort sensation		T	T	1
Palmar-plantar erythrodysesthesia syndrome	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL	Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self care ADL	-	-
	zed by redness, marked discomfort			reet.	1
Periorbital edema	Soft or non-pitting	Indurated or pitting edema; topical intervention indicated	Edema associated with visual disturbance; increased intraocular pressure, glaucoma or retinal hemorrhage; optic neuritis; diuretics indicated; operative intervention indicated	-	-
Definition: A disorder characteri	zed by swelling due to an excessive	e accumulation of fluid around the	orbits of the face.		
Photosensitivity	Painless erythema and erythema covering <10% BSA	Tender erythema covering 10 - 30% BSA	Erythema covering >30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (e.g., narcotics or NSAIDs)	Life-threatening consequences; urgent intervention indicated	Death

Skin and subcutaneous tissue disorders							
			Grade				
Adverse Event	1	2	3	4	5		
Pruritus	Mild or localized; topical intervention indicated	Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Intense or widespread; constant; limiting self care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated	-	-		
Definition: A disorder character	ized by an intense itching sensation		ı	I	'		
Purpura	Combined area of lesions covering <10% BSA	Combined area of lesions covering 10 - 30% BSA; bleeding with trauma	Combined area of lesions covering >30% BSA; spontaneous bleeding	- Dider lesions are usually a darker	- purple color		
and eventually become a brown				,			
Rash acneiform	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; lifethreatening consequences	Death		
Definition: A disorder character	ized by an eruption of papules and p	, oustules, typically appearing in fac	e, scalp, upper chest and back.	'	•		
Rash maculo-papular	Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering >30% BSA with or without associated symptoms; limiting self care ADL	-	-		
	ized by the presence of macules (fla upper trunk, spreading centripetally		nown as morbillform rash, it is one	of the most common cutaneous a	dverse		
Scalp pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-		
Definition: A disorder character	ized by marked discomfort sensation	n in the skin covering the top and	the back of the head.	ř			
Skin atrophy	Covering <10% BSA; associated with telangiectasias or changes in skin color	Covering 10 - 30% BSA; associated with striae or adnexal structure loss	Covering >30% BSA; associated with ulceration	-	-		
Definition: A disorder character	ized by the degeneration and thinnir	ng of the epidermis and dermis.		T			
Skin hyperpigmentation	Hyperpigmentation covering <10% BSA; no psychosocial impact	Hyperpigmentation covering >10% BSA; associated psychosocial impact	-	-	-		
Definition: A disorder character	ized by darkening of the skin due to	excessive melanin deposition.					
Skin hypopigmentation	Hypopigmentation or depigmentation covering <10% BSA; no psychosocial impact	Hypopigmentation or depigmentation covering >10% BSA; associated psychosocial impact	-	-	-		
Definition: A disorder character	ized by loss of skin pigment.						
Skin induration	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration, unable to slide or pinch skin; limiting joint movement or orifice (e.g., mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death		
Definition: A disorder character	ized by an area of hardness in the s		T	Γ			
Skin ulceration	Combined area of ulcers <1 cm; nonblanchable erythema of intact skin with associated warmth or edema	Combined area of ulcers 1 - 2 cm; partial thickness skin loss involving skin or subcutaneous fat	Combined area of ulcers >2 cm; full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may	Any size ulcer with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures with or	Death		

	Sk	in and subcutaneous tis	sue disorders					
	Grade							
Adverse Event	1	2	3	4	5			
Stevens-Johnson syndrome	-	-	Skin sloughing covering <10% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment)	Skin sloughing covering 10 - 30% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment)	Death			
Definition: A disorder characteriz	ed by less than 10% total body ski	in area separation of dermis. The	syndrome is thought to be a hyper	sensitivity complex affecting the s	kin and the			
mucous membranes.			_	_				
Telangiectasia	Telangiectasias covering <10% BSA	Telangiectasias covering >10% BSA; associated with psychosocial impact	-	-	-			
Definition: A disorder characteriz	ed by local dilatation of small vess	els resulting in red discoloration o	f the skin or mucous membranes.					
Toxic epidermal necrolysis	-	-	-	Skin sloughing covering >=30% BSA with associated symptoms (e.g., erythema, purpura, or epidermal detachment)	Death			
	ed by greater than 30% total body	skin area separation of dermis. T	he syndrome is thought to be a hy	persensitivity complex affecting th	e skin and the			
mucous membranes.			I					
Urticaria	Urticarial lesions covering <10% BSA; topical intervention indicated	Urticarial lesions covering 10 - 30% BSA; oral intervention indicated	Urticarial lesions covering >30% BSA; IV intervention indicated	-	-			
Definition: A disorder characteriz	ed by an itchy skin eruption chara	cterized by wheals with pale interi	ors and well-defined red margins.					
Skin and subcutaneous tissue disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death			

Social circumstances									
			Grade						
Adverse Event	1	2	3	4	5				
Menopause	Menopause occurring at age 46	Menopause occurring at age 40	Menopause occurring before	-	-				
	- 53 years of age	- 45 years of age	age 40 years of age						
Definition: A disorder characteriz	ed by the permanent cessation of	menses, usually defined by 12 co	nsecutive months of amenorrhea i	n a woman over 45 years of age.					
Social circumstances - Other,	Asymptomatic or mild	Moderate; minimal, local or	Severe or medically significant	Life-threatening consequences;	Death				
specify	symptoms; clinical or diagnostic	noninvasive intervention	but not immediately life-	urgent intervention indicated					
	observations only; intervention	indicated; limiting age-	threatening; hospitalization or						
	not indicated	appropriate instrumental ADL	prolongation of existing						
			hospitalization indicated;						
			disabling; limiting self care ADL						

Surgical and medical procedures								
	Grade							
Adverse Event	1	2	3	4	5			
Surgical and medical	Asymptomatic or mild	Moderate; minimal, local or	Severe or medically significant	Life-threatening consequences;	Death			
procedures - Other, specify	symptoms; clinical or diagnostic	noninvasive intervention	but not immediately life-	urgent intervention indicated				
	observations only; intervention	indicated; limiting age-	threatening; hospitalization or					
	not indicated	appropriate instrumental ADL	prolongation of existing					
			hospitalization indicated;					
1			disabling; limiting self care ADL					

		Vascular disord	ers		
			Grade		
Adverse Event	1	2	3	4	5
Capillary leak syndrome	-	Symptomatic; medical intervention indicated	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	ed by leakage of intravascular fluid syndromes, low-flow states, ischer			-	
Flushing	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Symptomatic, associated with hypotension and/or tachycardia; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by episodic reddening of the fa	ce.	1	1	1
Hematoma	Mild symptoms; intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by a localized collection of bloc	od, usually clotted, in an organ, sp	ace, or tissue, due to a break in th	e wall of a blood vessel.	
Hot flashes	Mild symptoms; intervention not indicated	instrumental ADL	Severe symptoms; limiting self care ADL	-	-
	ed by an uncomfortable and temp	orary sensation of intense body wa T	armth, flushing, sometimes accom		1
Hypertension	Prehypertension (systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg)	Stage 1 hypertension (systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg); medical intervention indicated; recurrent or persistent (>=24 hrs); symptomatic increase by >20 mm Hg (diastolic) or to	Stage 2 hypertension (systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated Pediatric: Same as adult	Death
		>140/90 mm Hg if previously WNL; monotherapy indicated Pediatric: recurrent or persistent (>=24 hrs) BP >ULN; monotherapy indicated	Pediatric: Same as adult		
Definition: A disorder characteriz	ed by a pathological increase in bl		,	ľ	1
Hypotension	indicated	Non-urgent medical intervention indicated	hospitalization indicated	Life-threatening and urgent intervention indicated	Death
Definition: A disorder characteriz	ed by a blood pressure that is belo	ow the normal expected for an indi	ividual in a given environment.	1	
Lymph leakage	-	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by the loss of lymph fluid into the	ne surrounding tissue or body cavi	ity.	1	1
Lymphedema	Trace thickening or faint discoloration	Marked discoloration; leathery skin texture; papillary formation; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by excessive fluid collection in	tissues that causes swelling.			
Lymphocele	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	-	-
Definition: A disorder characteriz	ed by a cystic lesion containing ly	nph.	1		
Peripheral ischemia	-	Brief (<24 hrs) episode of ischemia managed non- surgically and without permanent deficit	Recurring or prolonged (>=24 hrs) and/or invasive intervention indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A disorder characteriz	ed by impaired circulation to an ex	tremity.		_	
Phlebitis	-	Present	-	-	-
Definition: A disorder characteriz	ed by inflammation of the wall of a	vein. Present	-	-	-
	। ed by a blood clot and inflammatic	1	e extremities.	1	1

		Vascular disord	ers		
			Grade		
Adverse Event	1	2	3	4	5
Superior vena cava syndrome	Asymptomatic; incidental finding of SVC thrombosis	Symptomatic; medical intervention indicated (e.g., anticoagulation, radiation or chemotherapy)	Severe symptoms; multi- modality intervention indicated (e.g., anticoagulation, chemotherapy, radiation, stenting)	Life-threatening consequences; urgent multi-modality intervention indicated (e.g., lysis, thrombectomy, surgery)	Death
Definition: A disorder characteriz	ed by obstruction of the blood flow	in the superior vena cava. Signs	and symptoms include swelling ar	nd cyanosis of the face, neck, and	upper arms,
cough, orthopnea and headache			1	I	
Thromboembolic event	·		Thrombosis (e.g., uncomplicated pulmonary embolism [venous], non-embolic cardiac mural [arterial] thrombus), medical intervention indicated	Life-threatening (e.g., pulmonary embolism, cerebrovascular event, arterial insufficiency); hemodynamic or neurologic instability; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by occlusion of a vessel by a th	rombus that has migrated from a	distal site via the blood stream.		
Vasculitis	Asymptomatic, intervention not indicated	Moderate symptoms, medical intervention indicated	Severe symptoms, medical intervention indicated (e.g., steroids)	Life-threatening; evidence of peripheral or visceral ischemia; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by inflammation involving the w	rall of a vessel.			
Visceral arterial ischemia			Prolonged (>=24 hrs) or recurring symptoms and/or invasive intervention indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A disorder characteriz	ed by a decrease in blood supply	due to narrowing or blockage of a	visceral (mesenteric) artery.		
Vascular disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL	Severe or medically significant but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death







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APPENDIX 2. PEMPHIGUS DISEASE AREA INDEX (PDAI)

Pemphigus Disease Area Index (PDAI)

Skin	Activity		Damage						
Anatomical Locatio	Erosion/Blisters or new erythem	Post-inflammatory hyperpigmentation or erythema from resolving lesion							
	0 absent 1 1-3 lesions, up to one >2 cm in any diameter, none > 6 cm 2 2-3 lesions, at least two > 2 cm diameter, none > 6 cm 3 >3 lesions, none > 6 cm diameter 5 >3 lesions, and/or at least one >6 cm 10 >3 lesions, and/or at least one lesion >16 cm diameter or entire area	Number lesions if ≤ 3	0 absent 1 present						
Ears									
Nose									
Rest of the face									
Neck									
Chest									
Abdomen									
Back, buttocks									
Arms									
Hands			<u> </u>						
Legs									
Feet									
Genitals									
Total skin	/120		/12						
Scalp									
Scalp	Erosion/Blisters or new erythem	Post-inflammatory hyperpigmentation or erythema from resolving lesion							
	0 absent 1 in one quadrant 2 two quadrants 3 three quadrants 4 affects whole skull 10 at least one lesion > 6 cm	0 absent 1 present							
Total Scalp (0-10)	/10		/1						
Mucous men	nbrane								
Anatomical	Erosion/Blisters								
Location	0 absent 1 1 lesion 2 2-3 lesions 5 > 3 lesions or 2 lesions > 2 cm 10 entire area	Number lesions if ≤ 3							
Eyes									
Nose									
Buccal mucosa									
Hard palate									
Soft palate									
Upper gingiva									
Lower gingiva									
Tongue									
Floor of mouth									
Labial bucosa									
Posterior pharynx									
			I						
Anogenital		-	l .						

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APPENDIX 3. AUTOIMMUNE BULLOUS DISEASE QUALITY OF LIFE (ABQOL) QUESTIONNAIRE

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ABQOL Questionnaire

Name:	Date:
DOB: Sex: M/F	Contact Number:
Pemphigus Subtype: Pemphigus Vulgaris	 Epidermolysis Bullosa Aquisita
□ Bullous Pemphigoid	□ Linear IgA Bullous Dermatoses
□ Pemphigus Follaceus	□ Mucous Membrane Pemphigoid
□ Other	·
The following questions ask about the ways in quality of life.	which <i>blistering disease treatments</i> affect your
Please choose an option from the right hand co felt within the last week.	olumn which most closely correlates to how you
Please time your survey in minutes and se	conds – start time AM/PM
 In regards to your blistering disease, does your skin burn, sting or hurt in 	All the time Sometimes
any way?	Occasionally Not at all
2. In regards to your blistering disease,	All the time
does your skin itch?	SometimesOccasionally
	Not at all
Have you had to change your clothing because of your blictoring	I have to be very careful with how tight my elething is and what materials they
clothing because of your blistering disease?	my clothing is and what materials they are made of – I have had to change what I wear all the time
	I have had to change most of the things I wear
	I have had to change some of the things I wear
	I have never had to change what I wear
4. Do you notice your skin heals slowly?	I notice this all the time I notice this sometimes
	I notice this occasionally
Do you have difficulty bathing or	
showering because of your blistering	o Sometimes
disease?	Occasionally Not at all

In regards to your blistering disease, does your mouth have erosions which are painful?	All the timeSometimesOccasionallyNot at all
7. In regards to your blistering disease, do your gums bleed easily?	 All the time Sometimes Occasionally Not at all
Does your blistering disease results in you having to avoid food or drinks that you enjoy?	I can no longer eat any of the foods I used to enjoy I can eat some of the foods I enjoy I can eat most of the foods I enjoy I can eat anything I like
9. As a result of your blistering disease, are you embarrassed about your appearance?	 All the time Sometimes Occasionally Not at all
10. Do you feel depressed or angry because of your blistering disease?	 All the time Sometimes Occasionally Not at all
11. Do you feel anxious or cannot relax as a result of your blistering disease?	 All the time Sometimes Occasionally Not at all
12. Do you worry that friends and family find your blistering skin condition tiresome?	 All the time Sometimes Occasionally Not at all
13. Is your blistering disease causing sexual difficulties?	 All the time Sometimes Occasionally Not at all
14. Does your blistering disease affect relationships with friends or loved ones?	 I have had to end a relationship because of my disease OR I cannot have a relationship because of my disease Relationships are very difficult Relationships are a little difficult This has not affected my relationships

15. Does your blistering disease affect your social life?	 I cannot go out to socialize any more I can only go to some social events I can go to most social events My social life is not affected
16. Does your blistering disease affect your work or study?	 Yes, I can no longer work or study Yes, I find it difficult to work or study Yes, it is a little harder than before to work or study No, I am not affected OR not applicable (N/A)
17. Do employers discriminate against you because of your blistering disease?	I cannot find a job due to my blistering disease I have had to change jobs due to my blistering disease I still have my job but it is more difficult than before My employers are completely understanding OR not applicable (N/A)

Please indicate the time taken to finish the survery: minutes seconds

Thank you for taking the time to complete this questionnaire

APPENDIX 4. SKINDEX-29

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DERMATOLOGY SURVEY

This survey concerns the skin condition which has bothered you the most during the past four weeks.

These questions concern your feelings over the past 4 weeks about **the skin condition that has bothered you the most**. Check the answer that comes closest to the way you have been feeling.

HOW OFTEN DURING THE PAST FOUR WEEKS DO THESE STATEMENTS DESCRIBE YOU?	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE
1. My skin hurts	1	\square_2	Пз	□4	□5
2. My skin condition affects how well I sleep	\square_1	\square_2	\square_3	\square_4	\square_5
3. I worry that my skin condition may be serious	\square_1	\square_2	\square_3	\square_4	□5
4. My skin condition makes it hard to work or do hobbies	□₁	\square_2	\square_3	\square_4	\square_5
5. My skin condition affects my social life	\square_1	\square_2	\square_3	\square_4	□5
6. My skin condition makes me feel depressed	\square_1	\square_2	\square_3	\square_4	□5
7. My skin condition burns or stings	\square_1	\square_2	\square_3	\square_4	□5
8. I tend to stay at home because of my skin condition	\square_1	\square_2	\square_3	\square_4	\square_5
9. I worry about getting scars from my skin condition	\square_1	\square_2	□₃	\square_4	\square_5
10. My skin itches	\square_1	\square_2	Пз	\square_4	\square_5
11. My skin condition affects how close I can be with those I love .	\square_1	\square_2	Пз	\square_4	\square_5
12. I am ashamed of my skin condition	\square_1	\square_2	\square_3	\square_4	\square_5
13. I worry that my skin condition may get worse	\square_1	\square_2	Пз	\square_4	\square_5
14. I tend to do things by myself because of my skin condition .	\square_1	\square_2	Пз	\square_4	\square_5
15. I am angry about my skin condition	\square_1	\square_2	Пз	\square_4	\square_5
16. Water bothers my skin condition (bathing, washing hands) .	\square_1	\square_2	Пз	\square_4	\square_5
17. My skin condition makes showing affection difficult	\square_1	\square_2	Пз	\square_4	\square_5
18. I worry about side-effects from skin medications / treatments .	\square_1	\square_2	Пз	\square_4	\square_5
19. My skin is irritated	□1	\square_2	Пз	\square_4	\square_5
20. My skin condition affects my interactions with others	□1	\square_2	\square_3	\square_4	□5

Please turn to next page

These questions concern your feelings over the past 4 week about **the skin condition that has bothered you the most**. Check the answer that comes closest to the way you have been feeling.

HOW OFTEN DURING THE PAST 4 WEEK DO THESE STATEMENTS DESCRIBE YOU?	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE TIME
21. I am embarrassed by my skin condition	□ 1	\square_2	Пз	□4	\square_5
22. My skin condition is a problem for the people I love	□₁	\square_2	\square_3	\square_4	\square_5
23. I am frustrated by my skin condition	□1	\square_2	□₃	\square_4	\square_5
24. My skin is sensitive	□1	\square_2	□з	\square_4	\square_5
25. My skin condition affects my desire to be with people	□1	\square_2	\square_3	\square_4	\square_5
26. I am humiliated by my skin condition	□1	\square_2	\square_3	\square_4	\square_5
27. My skin condition bleeds	□₁	\square_2	\square_3	\square_4	\square_5
28. I am annoyed by my skin condition	□1	\square_2	\square_3	□4	\square_5
29. My skin condition interferes with my sex life	□1	\square_2	\square_3	\square_4	□5
30. My skin condition makes me tired	□₁	\square_2	□₃	\square_4	□5

APPENDIX 5. COHORT 2 ALTERNATE SCHEDULE OF EVENTS TABLE

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Table 10. Study Assessments for Cohort 2 (Alternate Weekly Dosing Option)

	Screening	Loa	ading			Maintenance								F	ollow-U	Ú p	
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Time Point (Study Day)	-14 to -1	0 Baseline	7 (±1 d)	14 (±1 d)	21 (±3 d)	28 (±3 d)	35 (±3 d)	42 (±3 d)	49 (±3 d)	56 (±3 d)	63 (±3 d)	70 (±3 d)	77 (±3 d)	84 (±3 d)	91 (±5 d) or ET Visit	112 (±5 d)	140 (±5 d) EOS Visit
Informed consent	X																
Demographics/medical history	X																
Inclusion/exclusion	X																
Physical examination ^a	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Vital signs ^b	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pulse oximetry ^c		X	X	X	X	X	X	X	X	X	X	X	X	X			
Clinical safety labs ^d	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test ^e	X	X			X										X		X
Hepatitis and HIV screen	X																
12-lead ECG ^f	X	X		X	X										X		X
Tetanus and VZV antibodies ^g		X			X										X		X
PDAI ^h	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK sampling ⁱ		X	X	X	X		X							X			
Immunogenicity ^j	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug administration ^k		X	X	X	X	X	X	X	X	X	X	X	X	X			
Immunoglobulins (IgG, IgA, IgM) and IgG subtypes (IgG1-4) ^l	X	X	X	Х	Х	Х	X	X	X	Х	X	X	X	X	X	X	X^q
CIC		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-Dsg (1 and 3) antibody titers	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C3 and AECA ^m	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FCGR2A by buccal swab ⁿ		X															
RNA sequencing		X			X										X		
Immunophenotyping°		X			X										X		
Exploratory pemphigus immune response biomarkers		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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Photography ^p	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HR-QoL assessments	X			X										X		X
Adverse events	To be collected from the date that the ICF is signed through the last study visit															
Concomitant medications	To be collected from within 14 days prior to Day 0 through the last study visit															

CIC = circulating immune complexes; d = day(s); ECG = electrocardiogram; EOS = end of study; ET= early termination; FCGR2A = Fc gamma R2a receptor; HIV = human immunodeficiency virus; HR-QoL = health-related quality of life; ICF = informed consent form; Ig = immunoglobulin; PDAI = Pemphigus Disease Area Index; PK = pharmacokinetic; VZV = varicella-zoster virus

- a. Complete physical examination, including weight, to be performed. Height and body mass index will be additional assessments conducted at screening only.
- b. **Vital sign** measurements (sitting blood pressure, heart rate, respiratory rate, and oral temperature) to be obtained after 5 minutes of seated rest. Any abnormal measurements are to be repeated after 5 minutes of rest. Vital sign measurements will be taken on all study visits. On dosing days, vital sign measurements will be collected immediately prior to the infusion; 15, 30, and 45 minutes after the start of the infusion; at completion of the infusion; and 30 minutes, 1 hour and 2 hours following completion of the infusion.
- c. **Pulse oximetry:** On dosing days, pulse oximetry to be measured immediately prior to the infusion; 15, 30, and 45 minutes after the start of the infusion; at completion of the infusion; and 30 minutes, 1 hour, and 2 hours following completion of the infusion.
- d. Clinical safety labs: hematology, clinical chemistry, and urinalysis. See Section 7.5 for a complete list. Full clinical safety lab draws will be collected at screening and at all study visits prior to infusion if applicable.
- e. **Pregnancy test (women of childbearing potential only):** To be performed at time of screening and prior to dose on dosing days if applicable. Urine or serum test is acceptable; however, positive urine tests must be confirmed with serum testing.
- f. Digital 12-lead ECG to be obtained after 5 minutes of rest in the supine position and in triplicate approximately 1 minute apart. See Section 7.6 for additional information. On dosing days, to be obtained approximately 5 minutes after the completion of infusion.
- g. **Serology:** Any subject whose baseline value for tetanus or VZV was above the protective level at baseline and is not within 30% of the baseline value or is below the protective level by End of Follow-up, will be referred to their primary care physician for further management. See Section 7.5.3 for additional information.
- h. PDAI will be administered at screening. Subject eligibility requires a PDAI total activity score >4. Thereafter, assuming eligibility, the PDAI will be administered during Treatment Period and Follow-up Period. See Section 7.7 for additional information.
- i. **PK:** On dosing days if applicable, serum samples will be collected just prior to the start of study drug infusion (pre-dose) and at 5 minutes, 1 and 2 hours after the end of study drug infusion. See Section 7.5.4 for additional information.
- j. Immunogenicity: Samples will be collected pre-dose when collected on dosing days. See Section 7.5.6 for additional information.
- k. Prior to **study drug infusion**, SYNT001 drug product is to be diluted in dextrose 5% in water to a total volume of 250 mL and administered intravenously over 1 hour ±15 minutes using a 0.2-micron, inline filter. See Section 4 for additional information.
- 1. Immunoglobulins (IgG, IgA, IgM) and IgG subtypes (IgG 1-4): Collected for measurements of IgG, IgG subtypes (IgG1-4), IgA, and IgM at every visit. On dosing days, samples are collected prior to infusion of study drug. See Section 7.5.5 for additional information.
- m. Exploratory pharmacodynamic samples (C3 and AECA): Collected pre-dose when collected on dosing days. See Section 7.5.5 for complete information.
- n. Buccal samples to be collected pre-dose.
- o. **Immunophenotyping** by flow cytometry for measurement of CD3⁺CD4⁺ T, CD3⁺CD8⁺ T, monocytes, natural killer (NK) cells, and B cells. Collect samples pre-dose on dosing days.
- p Photographs of all active lesions taken pre-dose on dosing days. Subjects who begin a steroid taper will have additional photographs taken at the clinic visit during which the decision to begin the taper is made.
- q Subjects whose total IgG is not within 30% of their Day 0 baseline value and not above 500 mg/dL at Day 140 will be referred for further management.

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PROTOCOL AMENDMENT **SUMMARY OF CHANGES**

Protocol Title: A Phase 1b/2, Multicenter, Open-Label, Safety, and Dose-Finding Study of

SYNT001 in Subjects with Pemphigus (Vulgaris or Foliaceus)

Protocol Number: SYNT001-103

Study Drug: SYNT001

Sponsor: Syntimmune, Inc.

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Original Protocol: 18 January 2017 21 March 2017 **Amendment 1.0:** Amendment 2.0 12 April 2017 Amendment 3.0 10 October 2017 Amendment 4.0 08 June 2018

Amendment 5.0 18 September 2018

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BACKGROUND

Protocol amendment Version 5.0 of the SYNT001-103 protocol was issued on 18 September 2018.

Syntimmune is amending the SYNT001-103 protocol to adjust the dosing schedule and cohort options. Because enrollment in Cohort 1 is complete, subjects will be enrolled in Cohort 2 which will now evaluate 3 weekly loading doses followed by 5 every other week maintenance doses, with the option to adjust to weekly dosing, if needed. Most updates in the amendment were incorporated to reflect this change, as well as refine how the ongoing safety of subjects in Cohort 2 would be monitored. The number of sites was increased to aid in enrollment and PDAI and photography assessments are now included at every post-treatment visit for Cohort 2 to better assess efficacy. PDAI also assessment added at screening for Cohort 2.

General grammatical, typographical, and formatting updates have been made throughout the document to provide consistency and clarity, reduce redundancy, and improve readability. These changes are not detailed in the summary below. Please see Amendment 5 for details.

SUMMARY OF CHANGES

With this update, the following changes since Version 4.0 have been made:

Table 1. Summary of Changes: Protocol Version 5.0

Section Number and Title	Description of Change
Sponsor Signature	The name of the Sponsor Representative has been updated.
Section 1, Protocol Synopsis	Below is a summary of changes to the protocol synopsis; refer to the changes described for the individual protocol sections for more detail: • Increased the number of study sites from 10 to 20 global sites to support subject enrollment.
	Study objectives and endpoints were updated to reflect changes to the dosing regimen (every other week in maintenance phase), to clarify that serum is used for pharmacokinetic analyses, and to update how analysis summaries will be presented.
	 The Study design and Methodology sections have been merged. The Study design not only describes changes to cohorts but also includes the role of the Dose Escalation Committee (DEC), Sponsor Medical Lead, and stopping and dose escalation rules.
	• The Number of subjects section has been updated to reflect the changes in the number of subjects and that Cohort 1 may enroll "up to" 8 subjects and Cohort 2 may enroll "up to" 12 subjects.
	The Study population section was modified to better define the population.
	• Inclusion criterion #4a was updated to reduce the last previous dose of rituximab or other anti-CD20 monoclonal antibodies from >12 months to >9 months prior to screening.
	• Inclusion criterion #9 was updated to reflect that male subjects are only required to use contraception through the final study visit.
	 Exclusion criterion #12 was updated to specify "at screening." Additional detail regarding dose/cohort changes has been added to Study drug, dosage, and administration and Duration of subject participation sections.
	More detail was added for clarity regarding corticosteroids.
	• In the statistical consideration section, analyses have been updated to reflect changes to the dosing regimen (every other week in maintenance phase) and to update how analysis summaries will be presented.
Study Diagram	Study Diagram has been added for clarity around the changes to study design and the reduction in the number of cohorts to 2.

	• Cohort 2 has been modified to 3 weekly loading doses of 30 mg/kg followed by 5 every other week doses of 10 mg/kg and the number of subjects enrolled will be up to 12.
	The original Cohort 2 and optional Cohort 4 were removed.
	• The Sponsor Medical Team will conduct the 24-hour and 7-day safety reviews for subjects in Cohort 2.
	• Ongoing safety review may result in may modified dosing regimen (e.g. 10 weekly maintenance doses at 10-30 mg/kg).
Schedule of Events	Tables 3 and 4 (original Cohort 2 and Cohort 3) were deleted.
	Table 3 (Cohort 2): This table reflects a new dosing schedule with loading and maintenance doses, as well as the increase of PDAI and photography assessments to every post-treatment visit. PDAI also added at screening. See Table 3 for details.
List of Abbreviations	The table was updated to include all abbreviations throughout the synopsis and protocol text. Each abbreviation was defined the first time used in both the synopsis and protocol text.
Section 2,	Background and Rationale
Background and Rationale	Text has been added to describe SYNT001's predicted mechanism of action
	Additional indications identified as IgG-mediated autoimmune disorders have been removed
	Selection of Doses in this Study
	Details of mathematical modeling of study dose selection were added.
	Details of non-clinical and clinical studies supporting the proposed Cohort 2 dose and dosing regimen were added.
Section 3, Study Objectives and Endpoints	• Study objectives and endpoints were updated to reflect changes to the dosing regimen (every other week in maintenance phase), to clarify that serum is used for pharmacokinetic analyses, and to update how analysis summaries will be presented.
Section 4, Study	 The secondary objectives were reordered to reflect their importance. Description of SYNT001
Drug	Added that Investigators are allowed to adjust the duration of the infusion to increase tolerability up to 4 hours, if needed.
	 Dose Requirements It has been clarified that subject doses will be limited to 5000 mg. A subject with a body weight that extrapolates to a dose > 5000 mg, will only receive 5000 mg.
Section 5, Study	The number of study sites was increased from 10 to 20.
Design	The study design has been updated to reflect changes in dosing regimen for Cohort 2.
	• Cohort 1 number of subjects has been modified from 8 to <u>up to</u> 8.

	• Cohort 2 has been modified to 3 weekly loading doses of 30 mg/kg followed by 5 every other week doses of 10 mg/kg and the number of subjects enrolled will be up to 12.
	Original Cohort 2 and optional Cohort 3 were removed.
	• The Sponsor Medical Team will conduct the 24-hour and 7-day safety reviews for Cohort 2.
	• Ongoing safety review may result in may modified dosing regimen (e.g. 10 weekly maintenance doses at 10-30 mg/kg).
	• Duration of Subject Participation was added to the body of the protocol for consistency with the synopsis.
Section 6, Study Population	 Target Population Based on the new study design, the total number of subjects has been changed to a maximum of 20 subjects, but the number is not included in this section, just a description of the study population. Inclusion Criteria
	• Inclusion criterion #4a was updated to reduce the last previous dose of rituximab or other anti-CD20 monoclonal antibodies from >12 months to >9 months prior to screening.
	• Inclusion criterion #9 was updated to reflect that male subjects are only required to use contraception through the final study visit.
	Exclusion Criteria
~ ~ .	• Exclusion criterion #12 was updated to specify "at screening."
Section 7, Study Procedures	• References to specific days have been removed because of the addition of the separate Cohort 2 table and possibility of following the optional weekly schedule in Appendix 3.
	• Virology assessments were removed from Table 6 because they are not included with clinical laboratory panels.
	• PK parameters studied in Cohort 1 differ from (the) successive cohort(s) and which include maximum serum concentration of SYNT001 and the associated T _{max} .
	• Pharmacodynamic Assessment (Table 7) has been updated to include timing of testing for Cohort 2
	A subsection re: corticosteroid use was added for clarity.
Section 8, Study Assessments	Sections were edited to reflect the updates to assessments performed in the new schedule of events for Cohort 2. See Section 8 for details.
Section 9, Study	Subject Withdrawal
Rules	Details were added to distinguish between follow up assessments for
	subjects who prematurely discontinue study drug versus subjects who
	 prematurely discontinue from the study. Details were added to specify which study visits the subject should be encouraged to attend in each case above.
	Stopping Rules

	• The description of dose escalation stopping rules now reflects that Cohort 2 will not be a dose escalation cohort.
	 Decisions regarding study stopping rules originally to be made by the DEC were updated to be decided by the Sponsor Medical Lead.
Section 10,	No substantial changes were made to this section; only updates to
Evaluation of	abbreviations and minor corrections for consistency.
Safety	Warnings and Precautions
	• Allowed vaccinations were updated to 28 days after the final dose of
	study drug rather than discretion of investigator.
Section 11,	"Data" was updated to "analysis" in headings.
Statistical	Details of analyses have been updated to reflect changes to the dosing
Considerations	regimen (every other week in maintenance phase) and to update how
	analysis summaries will be presented.
	Safety Analysis
	 More detail was added to the safety analyses to be performed.
	• Relationship of adverse events (AEs) to study drug was defined as in the AE section (related/not related).
	• The lab analyses were updated to be formed by a central laboratory. Pharmacokinetic Analysis
	 PK and PD analyses were moved to separate sections.
	 Details were made more general to cover different analyses performed in the 2 cohorts.
	Pharmacodynamic (PD) Analysis
	• Details of the presentation of disease activity marker results were added.
Sections 12-14	No edits other than global changes mentioned below.
Appendix 5	Appendix was added to include an alternate schedule of events for Cohort 2 (weekly dosing)
Global Changes	Edits and formatting changes have been made throughout to improve clarity and readability.
	• Typographical and formatting corrections as well as corrections for consistency have been made.