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
Medical Monitor:	PPD 43 Thorndike Street, Cambridge, MA 01240 Phone: PPD extension PPD Mobile: PPD
Original Protocol:	18 January 2017

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 dial PPD or PPD PPD dial PPD Facsimile: PPD or PPD PPD	PPD PPD Mobile phone PPD Office phone: ext. PPD

SAE CRITERIA

* A serious adverse event (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.

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: 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) **Exploratory objectives** • 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) o 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 ≥ 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 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 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; 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; 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, and administration	SYNT001 **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 70 days (10 weeks): Screening of up to 2 weeks (14 days); dosing period of 4 weeks (28 days); and 4 weeks (28 days) of follow-up

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 (*FCGR2A* 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}, $AUC_{0-24,}$ and $AUC_{0-\infty.}$
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[l]		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.*																

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

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
l: 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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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

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:
  - 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)

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:
  - Serum anti-epithelial cell antibody (AECA) levels by indirect immunofluorescence
  - Circulating immune complexes (CIC)
  - 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

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 (AUC_{0-24}), and area under the plasma concentration-time curve from pre-dose (time 0) to infinity ($AUC_{0-\infty}$)

PD Biomarkers:

- Ig Assessments: Serial assessments of total IgG and IgG subtypes (IgG1-4)
  - Serial assessments of total IgG and IgG subtypes (IgG1-4)
  - IgA levels
  - 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 ≥ 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 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;
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 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 $\leq$ 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 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.

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

7.10 Treatment Day 21 (Dose 4)

On Day 21, (± 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
- 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 (± 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 ± 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 ± 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 ± 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 (± 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 (± 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 ≥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 ± 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 (2ºC to 8ºC/36ºF to 46ºF) 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 5).

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

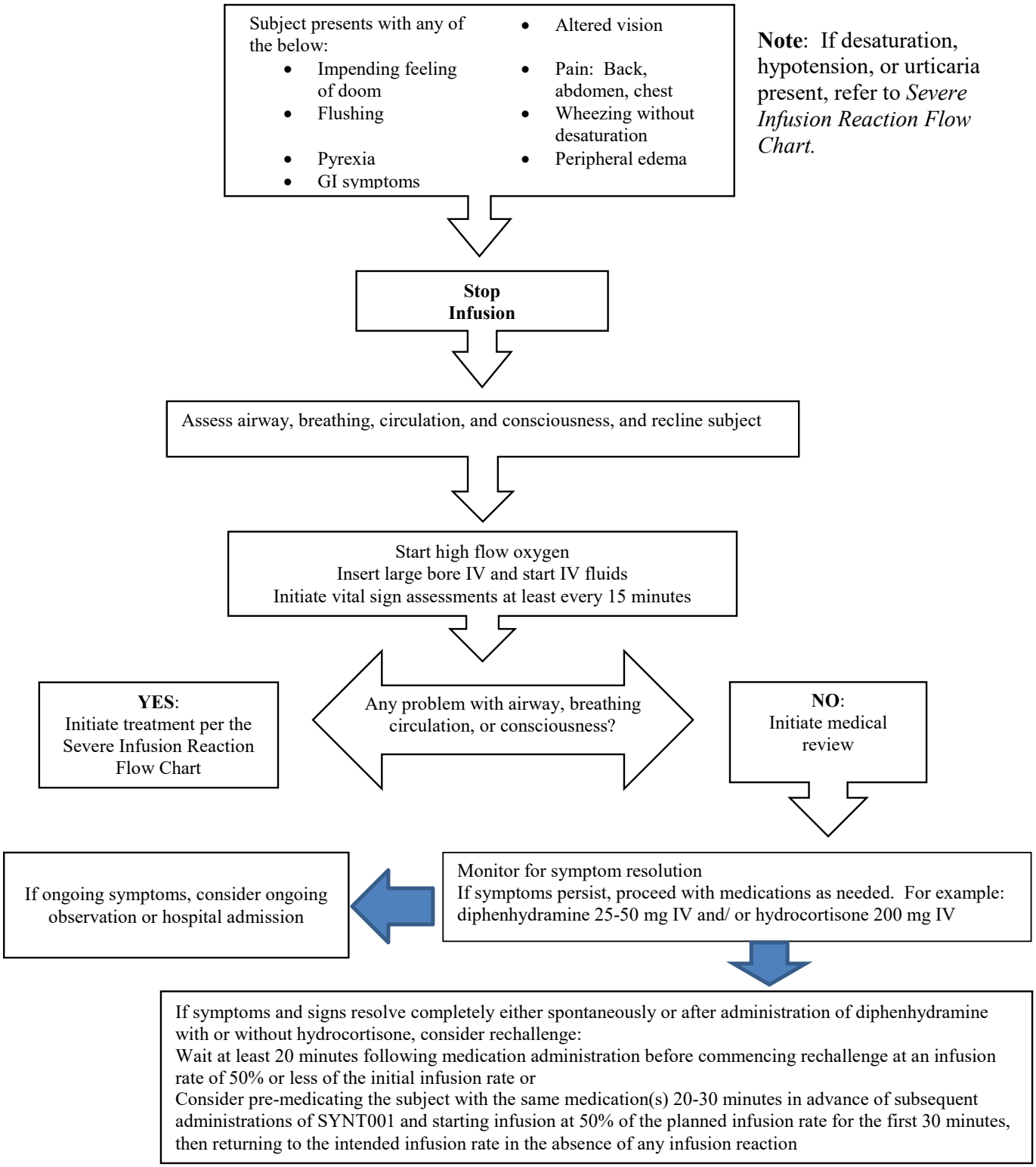

Figure 2: Management of Severe (Grade 3 or higher) Infusion Reactions

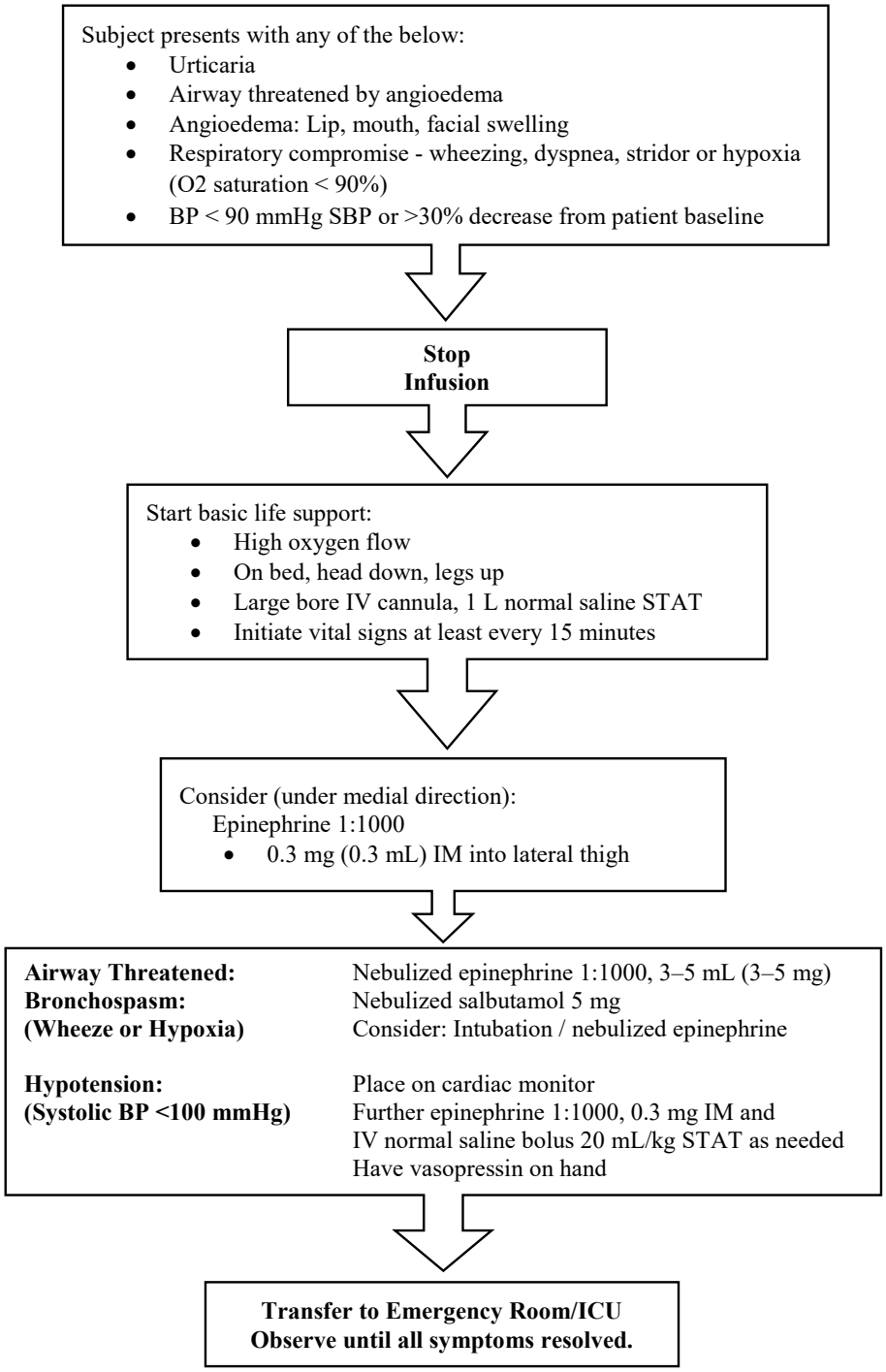

Table 5: Grading and Management of Allergic or Infusion-Related Reactions

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:

- **Death:** 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.

- **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:**
  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**
- **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.

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 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:

Medpace Clinical Safety
Medpace SAE hotline:
Telephone: PPD dial PPD or PPD dial PPD
Facsimile: PPD or PPD
e-mail PPD

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

Medical Safety Contact
PPD
Phone (US): PPD extension PPD
Mobile phone: PPD
Email: PPD

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

Sponsor Contact:	PPD PPD Phone:PPD Email:
Sponsor Medical Director:	PPD PPD Phone:PPD Email:
Medical Monitor:	PPD Medpace 43 Thorndike Street Cambridge, MA 01240 Phone:PPD ext.PPD Email:PPD
Study Monitoring:	Medpace 5375 Medpace Way Cincinnati, OH 45227 Phone (Main):PPD Email: PPD

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

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 *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 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).

CONTENTS

Blood and lymphatic system disorders					
	Grade				
Adverse Event	1	2	3	4	5
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	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
Definition: A disorder characterized by an reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.					
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 characterized by the inability of the bone marrow to produce hematopoietic elements.					
Disseminated intravascular coagulation	-	Laboratory findings with no bleeding	Laboratory findings and bleeding	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by systemic pathological activation of blood clotting mechanisms which results in clot formation throughout the body. There is an increase in the risk of hemorrhage as the body is depleted of platelets and coagulation factors.					
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 characterized by an ANC <1000/mm3 and 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.					
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 characterized by laboratory test results that indicate widespread erythrocyte cell 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 characterized by a form of thrombotic microangiopathy with renal failure, hemolytic anemia, and severe thrombocytopenia.					
Leukocytosis	-	-	>100,000/mm3	Clinical manifestations of leucostasis; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate an increased number of white blood cells in the blood.					
Lymph node 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 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 spleen.					
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
Definition: A disorder characterized by the presence of microangiopathic hemolytic anemia, thrombocytopenic purpura, fever, renal abnormalities and neurological abnormalities such as seizures, hemiplegia, and visual disturbances. It is an acute or subacute condition.					
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
Definition: A disorder characterized by signs and symptoms related to acute ischemia of the myocardium secondary to coronary artery disease. The clinical presentation covers a spectrum of heart diseases from unstable angina to myocardial infarction.					
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 characterized by a defect in aortic valve function or structure.					
Asystole	Periods of asystole; non-urgent medical management indicated	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia without cardiac electrical activity. Typically, this is accompanied by cessation of the 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 characterized by a dysrhythmia without discernible P waves and an irregular ventricular response due to multiple reentry circuits. The rhythm disturbance originates above the ventricles.					
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 characterized by a dysrhythmia with organized rhythmic atrial contractions with a rate of 200-300 beats per minute. The rhythm disturbance originates in the atria.					
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 characterized by a dysrhythmia with complete 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	-	-	-
Definition: A disorder characterized by a dysrhythmia with a delay in the time required for the conduction of an electrical impulse through the atrioventricular (AV) node beyond 0.2 seconds; prolongation of the PR interval greater than 200 milliseconds.					
Cardiac arrest	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by cessation of the pumping function of the heart.					
Chest pain - cardiac	Mild pain	Moderate pain; limiting instrumental ADL	Pain at rest; limiting self care ADL	-	-
Definition: A disorder characterized by substernal discomfort due to insufficient myocardial oxygenation.					
Conduction disorder	Mild symptoms; intervention not indicated	Moderate symptoms	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized 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 characterized by a thickened and fibrotic pericardial sac; these fibrotic changes impede normal myocardial function by restricting myocardial muscle 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 support)	Death
Definition: A disorder characterized by the inability of the heart to pump blood at an adequate volume to meet tissue metabolic requirements, or, the ability to do so only at an elevation in the filling pressure.					

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
Definition: A disorder characterized by failure of the left ventricle to produce adequate output despite an increase in distending pressure and in end-diastolic volume. Clinical manifestations mayinclude dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.					
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 characterized by a defect in mitral valve function 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
Definition: A disorder characterized by a dysrhythmia with relatively constant PR interval prior to the block of an atrial impulse. This is the result of intermittent failure of atrial electrical impulse conduction through the atrioventricular (AV) node to the ventricles.					
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
Definition: A disorder characterized by a dysrhythmia with a progressively lengthening PR interval prior to the blocking of an atrial impulse. This is the result of intermittent failure of atrial electrical impulse conduction through the atrioventricular (AV) node to the ventricles.					
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 characterized by gross necrosis of the myocardium; this is due to an interruption 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 characterized by inflammation of the muscle tissue of the heart.					
Palpitations	Mild symptoms; intervention not indicated	Intervention indicated	-	-	-
Definition: A disorder characterized by an unpleasant sensation of irregular and/or forceful beating of 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 characterized by a dysrhythmia with abrupt onset and sudden termination of atrial contractions with a rate of 150-250 beats per minute. The rhythm disturbance originates in the atria.					
Pericardial effusion	-	Asymptomatic effusion size small to moderate	Effusion with physiologic consequences	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by fluid collection within the pericardial sac, usually due to inflammation.					
Pericardial tamponade	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in intrapericardial pressure due to the collection of blood or fluid in the pericardium.					
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
Definition: A disorder characterized by irritation to the layers of the pericardium (the protective sac around the heart).					

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 characterized by a defect in pulmonary valve function or structure.					
Restrictive cardiomyopathy	-	-	Symptomatic heart failure or other cardiac symptoms, responsive to intervention	Refractory heart failure or other poorly controlled cardiac symptoms	Death
Definition: A disorder characterized by an inability of the ventricles to fill with blood because the myocardium (heart muscle) stiffens and loses its flexibility.					
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 characterized by impairment of right ventricular function associated with low ejection fraction and a decrease in motility 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
Definition: A disorder characterized by a dysrhythmia with alternating periods of bradycardia and atrial tachycardia accompanied by syncope, fatigue and dizziness.					
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 characterized by a dysrhythmia with a heart rate 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 characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates in the sinus node.					
Supraventricular tachycardia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates above the ventricles.					
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 characterized by a defect in tricuspid valve function 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 characterized by a dysrhythmia that originates in the ventricles.					
Ventricular fibrillation	-	-	-	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia without discernible QRS complexes due to rapid repetitive excitation of myocardial fibers without coordinated contraction of the ventricles.					
Ventricular tachycardia	-	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates distal to the bundle 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 characterized by the presence of an accessory conductive pathway between the atria and the ventricles that causes premature ventricular activation.					
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 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 characterized by a sensation of marked discomfort 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 characterized by inflammation, swelling and redness to the outer ear and ear canal.					
External ear 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 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 aids; threshold shift >20 dB at 3 kHz and above in at least one ear; additional speech-language related services indicated.	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.	-
Definition: A disorder characterized by partial or complete loss of the ability to detect or understand sounds resulting from damage to ear structures.					
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
Definition: A disorder characterized by inflammation (physiologic response to irritation), swelling and redness to the middle ear.					
Tinnitus	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by noise in the ears, such as ringing, buzzing, roaring or clicking.					
Vertigo	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation as if the external world were revolving around the patient (objective vertigo) or as if he himself were revolving in space (subjective vertigo).					
Vestibular disorder	-	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dizziness, imbalance, nausea, 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	Moderate symptoms; medical intervention indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder that occurs when the adrenal cortex does not produce enough of the hormone cortisol and in some cases, the hormone aldosterone. It may be due to a disorder of the adrenal cortex as in Addison's disease or primary adrenal insufficiency.					
Cushingoid	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms, medical intervention or hospitalization indicated	-	-
Definition: A disorder characterized by signs and symptoms that resemble Cushing's disease or syndrome: buffalo hump obesity, striations, adiposity, hypertension, diabetes, and osteoporosis, usually due to exogenous corticosteroids.					
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 characterized by unusually late sexual maturity.					
Growth accelerated	-	>= +2 SD (standard deviation) above mid parental height or target height	-	-	-
Definition: A disorder characterized by greater growth than expected for age.					
Hyperparathyroidism	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by an increase in production of parathyroid hormone by the parathyroid glands. This results in hypercalcemia (abnormally high levels of calcium in the blood).					
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 characterized by excessive levels of thyroid hormone in the body. Common causes include an overactive thyroid gland or thyroid hormone overdose.					
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 characterized by a decrease in production of parathyroid hormone by the parathyroid 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 characterized by a decrease in production of thyroid hormone by the thyroid gland.					
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 characterized by unusually early development of secondary sexual features; the onset of sexual maturation begins usually before age 8 for girls and before age 9 for boys.					
Virilization	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by inappropriate masculinization occurring in a female or prepubertal 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 disorders					
	Grade				
Adverse Event	1	2	3	4	5
Blurred vision	Intervention not indicated	Symptomatic; limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by visual perception of unclear or fuzzy images.					
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., cataract surgery)	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by partial or complete opacity of the crystalline lens of one or both eyes. This results in a decrease in visual acuity and eventual blindness if untreated.					
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 characterized by inflammation, swelling and redness to the conjunctiva of the eye.					
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 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	Symptomatic; multiple agents indicated; limiting instrumental ADL	Decrease in visual acuity (<20/40); limiting self care ADL	-	-
Definition: A disorder characterized 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 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 characterized by a sensation of marked discomfort in the eye.					
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 characterized by impaired eyelid function.					
Flashing lights	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by a sudden or brief burst of light.					
Floaters	Symptomatic but not limiting ADL	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.					
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 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	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 characterized by inflammation to the cornea of the eye.					
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 characterized by an inability to see clearly in dim light.					

Eye disorders					
	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	-
Definition: A disorder characterized by involvement of the optic nerve (second cranial nerve).					
Papilledema	Asymptomatic; no visual field defects	Symptomatic decline in 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 characterized by swelling around the optic disc.					
Photophobia	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by fear and avoidance of 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 characterized by the separation of the inner retina layers from the underlying 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 characterized by a small laceration of the retina, this occurs when the vitreous separates from the retina. Symptoms include flashes and floaters.					
Retinal vascular disorder	-	Topical medication indicated	Intravitreal medication; operative intervention indicated	-	-
Definition: A disorder characterized by pathological retinal blood vessels that adversely affects 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 involving 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 characterized by involvement of the sclera of the eye.					
Uveitis	Asymptomatic; clinical or diagnostic observations only	Anterior uveitis; medical intervention indicated	Posterior or pan-uveitis	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by inflammation to the uvea of the eye.					
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 characterized by blood extravasation into the vitreous humor.					
Watering eyes	Intervention not indicated	Intervention indicated	Operative intervention indicated	-	-
Definition: A disorder of excessive tearing in the eyes; it can be caused by overproduction 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 disorders					
	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 characterized by swelling of the abdomen.					
Abdominal 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 abdominal region.					
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 characterized 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 characterized by bleeding from the anal region.					
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 characterized 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
Definition: A disorder characterized by a necrotic process occurring in the anal region.					
Anal 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 anal region.					
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 characterized 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 characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the anal canal.					
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 characterized by accumulation of serous or hemorrhagic 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 characterized by subject-reported feeling of uncomfortable fullness of the abdomen.					
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 characterized 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	-	-
Definition: A disorder characterized by inflammation of the lip.					

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
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 characterized 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 characterized 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 characterized by bleeding from the colon.					
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
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents in the colon.					
Colonic perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the colonic wall.					
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 characterized 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 characterized by a circumscribed, inflammatory 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 characterized by irregular and infrequent or difficult 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 characterized by the decay of a tooth, in which 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 characterized by frequent and watery bowel movements.					
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	-	-
Definition: A disorder characterized by reduced salivary flow in the oral cavity.					

Gastrointestinal disorders					
	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 characterized by an abnormal communication between the duodenum and another 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 characterized by bleeding from the duodenum.					
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 characterized 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 characterized by a rupture in the duodenal wall.					
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 characterized 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 characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the duodenal wall.					
Dyspepsia	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; surgical intervention indicated	-	-
Definition: A disorder characterized by an uncomfortable, often painful feeling in the stomach, resulting from impaired digestion. Symptoms include burning stomach, bloating, heartburn, nausea and vomiting.					
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 characterized by difficulty in swallowing.					
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 characterized by inflammation of the small and 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 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	Life-threatening consequences; urgent intervention indicated	Death
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 or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the esophagus.					

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 characterized by a necrotic process occurring 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 characterized by blockage of the normal flow of the contents in the esophagus.					
Esophageal 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 esophageal region.					
Esophageal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the wall of the esophagus.					
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 characterized 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 characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the esophageal 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 characterized by bleeding from esophageal varices.					
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 characterized by inflammation of the esophageal wall.					
Fecal incontinence	Occasional use of pads required	Daily use of pads required	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by inability to control the escape of stool from the rectum.					
Flatulence	Mild symptoms; intervention not indicated	Moderate; persistent; psychosocial sequelae	-	-	-
Definition: A disorder characterized by a state of excessive gas in the alimentary canal.					
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 characterized by an abnormal communication between the stomach and another organ or anatomic site.					
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 characterized by bleeding from the gastric wall.					
Gastric 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 characterized by a necrotic process occurring in the gastric wall.					

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Gastric perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the stomach wall.					
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 characterized 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
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the stomach.					
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 characterized by inflammation of the stomach.					
Gastroesophageal reflux disease	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; surgical intervention indicated	-	-
Definition: A disorder characterized by reflux of the gastric and/or duodenal contents into the distal esophagus. It is chronic in nature and usually caused by incompetence of the lower esophageal sphincter, and may result in injury to the esophageal mucosal. Symptoms include heartburn and acid indigestion.					
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 characterized by an abnormal communication between any part of the gastrointestinal 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 characterized by a sensation of marked discomfort in the gastrointestinal region.					
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 characterized by an incomplete paralysis of the muscles of the stomach wall resulting in delayed emptying of the gastric contents into the small intestine.					
Gingival pain	Mild pain	Moderate pain interfering with oral intake	Severe pain; inability to aliment orally	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the gingival region.					
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 characterized by bleeding from the hemorrhoids.					
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 characterized by the presence of dilated veins in the rectum and surrounding area.					
Ileal 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 characterized by an abnormal communication between the ileum and another organ or anatomic site.					
Ileal 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 characterized by bleeding from the ileal wall.					

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Ileal 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 characterized by blockage of the normal flow of the intestinal contents in the ileum.					
Ileal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the ileal wall.					
Ileal 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 characterized by a narrowing of the lumen of the ileum.					
Ileal 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 characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the ileum.					
Ileus	-	Symptomatic; altered GI function; bowel rest indicated	Severely altered GI function; TPN indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by failure of the ileum to transport intestinal contents.					
Intra-abdominal hemorrhage	-	Medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding in the abdominal cavity.					
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 characterized by an abnormal communication between the jejunum and another 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 characterized by bleeding from the jejunal wall.					
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 characterized by blockage of the normal flow of the intestinal contents in the jejunum.					
Jejunal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized 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 characterized 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 characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the jejunum.					
Lip pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort of the lip.					

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Lower 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 characterized by bleeding from the lower gastrointestinal 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 characterized by inadequate absorption of nutrients in the small intestine. Symptoms include abdominal marked 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 characterized by inflammation of the oral mucosal.					
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 characterized by a queasy sensation and/or the urge to vomit.					
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 characterized by blockage of the normal flow of the contents in the stomach.					
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 characterized by an abnormal communication between the oral cavity and another 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 characterized by a burning or tingling sensation on the lips, tongue or entire mouth.					
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 characterized by bleeding from the mouth.					
Oral 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 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 characterized 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 characterized by an abnormal communication between the pancreas and another organ or anatomic site.					
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 characterized by bleeding from the pancreas.					
Pancreatic necrosis	-	-	Tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized 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
Definition: A disorder characterized by inflammation of the pancreas.					
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 gingival 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 characterized 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 characterized 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 characterized by an abnormal communication 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 characterized 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 characterized 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 characterized 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 characterized by blockage of the normal flow of the intestinal contents in the rectum.					
Rectal 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 rectal region.					
Rectal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized 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 characterized 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
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the rectum.					

Gastrointestinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
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 characterized by bleeding from the retroperitoneal area.					
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 characterized 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 characterized by an abnormal communication between a salivary gland and another 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 characterized 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 characterized 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 characterized by a rupture in the small intestine 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 characterized 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 characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the small intestine.					
Stomach 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 stomach.					
Tooth development disorder	Asymptomatic; hypoplasia of tooth or enamel	Impairment correctable with oral surgery	Maldevelopment with impairment not surgically correctable; disabling	-	-
Definition: A disorder characterized by a pathological process of the teeth occurring during tooth development.					
Tooth discoloration	Surface stains	-	-	-	-
Definition: A disorder characterized by a change in tooth hue or tint.					
Toothache	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 tooth.					

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 characterized 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 characterized by bleeding from the upper gastrointestinal tract (oral cavity, pharynx, 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 characterized by the reflexive act of ejecting the contents of the stomach through 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

General disorders and administration site conditions					
	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 characterized by a sensation of cold that often marks a physiologic response to sweating after a fever.					
Death neonatal	-	-	-	-	Death
Definition: A disorder characterized by cessation of life occurring during 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 characterized by swelling due to excessive fluid 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 characterized by swelling due to excessive fluid accumulation in the upper or lower 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 characterized by swelling due to excessive fluid accumulation in the trunk area.					
Facial 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 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 characterized by a state of generalized weakness with a pronounced inability to summon sufficient energy to accomplish 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 characterized by elevation of the body's temperature above the upper limit of normal.					
Flu like symptoms	Mild flu-like symptoms present	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by a group of symptoms similar to those observed in patients with the flu. It includes fever, chills, body aches, malaise, loss of appetite and dry cough.					
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 characterized by walking difficulties.					
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
Definition: A disorder characterized by an abnormally low body temperature. Treatment is required when the body temperature is 35C (95F) or below.					

General disorders and administration site conditions					
	Grade				
Adverse 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 (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	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.					
Infusion site extravasation	-	Erythema with associated symptoms (e.g., edema, pain, induration, phlebitis)	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by leakage of a pharmacologic or a biologic substance from the infusion site into the surrounding tissue. Signs and symptoms include induration, erythema, swelling, burning sensation and marked discomfort at the infusion site.					
Injection site reaction	Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)	Pain; lipodystrophy; edema; phlebitis	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an intense adverse reaction (usually immunologic) developing at the site of an injection.					
Irritability	Mild; easily consolable	Moderate; limiting instrumental ADL; increased attention indicated	Severe abnormal or excessive response; limiting self care ADL; inconsolable	-	-
Definition: A disorder characterized by an abnormal responsiveness to stimuli or physiological arousal; may be in response to pain, fright, a drug, an emotional situation or a medical condition.					
Localized edema	Localized to dependent areas, no disability or functional impairment	Moderate localized edema and intervention indicated; limiting instrumental ADL	Severe localized edema and intervention indicated; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to excessive fluid accumulation at a specific anatomic site.					
Malaise	Uneasiness or lack of well being	Uneasiness or lack of well being; limiting instrumental ADL	-	-	-
Definition: A disorder characterized by a feeling of general discomfort or uneasiness, an out-of-sorts feeling.					
Multi-organ failure	-	-	Shock with azotemia and acid-base disturbances; significant coagulation abnormalities	Life-threatening consequences (e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic acidosis)	Death
Definition: A disorder characterized by progressive deterioration of the lungs, liver, kidney and clotting mechanisms.					
Neck edema	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	-	-
Definition: A disorder characterized by swelling due to an accumulation of excessive fluid in the neck.					
Non-cardiac chest pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by discomfort in the chest unrelated to a heart disorder.					
Pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by the sensation of marked discomfort, distress or agony.					
Sudden death NOS	-	-	-	-	Death
Definition: An unexpected cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.					
General disorders and administration site conditions - 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

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 characterized by a narrowing of the lumen of the bile duct.					
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 characterized by an abnormal communication between the bile ducts and another 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 characterized by inflammation involving the gallbladder. It may be associated with 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 characterized by an abnormal communication between the gallbladder and another organ or anatomic site.					
Gallbladder necrosis	-	-	-	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring 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
Definition: A disorder characterized by blockage of the normal flow of the contents of the gallbladder.					
Gallbladder 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 gallbladder region.					
Gallbladder perforation	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the gallbladder wall.					
Hepatic failure	-	-	Asterixis; mild encephalopathy; limiting self care ADL	Moderate to severe encephalopathy; coma; life-threatening consequences	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, lactic dehydrogenase, and alkaline phosphatase.					
Hepatic hemorrhage	Mild; intervention not indicated	Symptomatic; medical intervention indicated	Transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the liver.					
Hepatic necrosis	-	-	-	Life-threatening consequences; urgent radiologic or operative intervention 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 indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the wall of the extrahepatic or intrahepatic bile duct.					

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 characterized by an increase in blood pressure in the portal venous system.					
Portal vein thrombosis	-	Intervention not indicated	Medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized 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; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Immune system disorders					
	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
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.					
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and 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 from loss of function or tissue destruction of an organ or multiple organs, arising from humoral or cellular immune responses of the individual to his own tissue constituents.					
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 characterized by nausea, headache, tachycardia, hypotension, rash, and shortness 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
Definition: A disorder characterized by a delayed-type hypersensitivity reaction to foreign proteins derived from an animal serum. It occurs approximately six to twenty-one days following the administration of the foreign antigen. Symptoms include fever, arthralgias, myalgias, skin eruptions, lymphadenopathy, chest marked discomfort and dyspnea.					
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 infestations					
	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 characterized by an infectious process involving 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
Definition: A disorder characterized by an infectious process involving the anal area and the rectum.					
Appendicitis	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by acute inflammation to the vermiform appendix caused by a pathogenic agent.					
Appendicitis perforated	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by acute inflammation to the vermiform appendix caused by a pathogenic agent with gangrenous changes resulting in the rupture of the appendiceal wall. The appendiceal wall rupture causes the release of inflammatory and bacterial contents from the appendiceal lumen into the abdominal cavity.					
Arteritis infective	-	-	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 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 characterized by an infectious process involving 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 characterized by an infectious process involving 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 characterized by an infectious process involving the bones.					
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
Definition: A disorder characterized by an infectious process involving the breast.					
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 characterized by an infectious process involving 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 characterized 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 infestations					
	Grade				
Adverse Event	1	2	3	4	5
Definition: A disorder characterized by an infectious process involving 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
Definition: A disorder characterized by an infectious process involving the uterine cervix.					
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 characterized by an infectious process involving the conjunctiva. Clinical manifestations 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 characterized by an infectious process involving 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 characterized by an infectious process involving 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
Definition: A disorder characterized by an infectious process involving the use of a medical device.					
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 characterized by an infectious process involving 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 characterized by an infectious process involving the brain tissue.					
Encephalomyelitis infection	-	-	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 brain and spinal cord tissues.					
Endocarditis infective	-	-	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 endocardial layer of the heart.					
Endophthalmitis	-	Local intervention indicated	Systemic intervention or hospitalization indicated	Blindness (20/200 or worse)	-
Definition: A disorder characterized by an infectious process involving the internal structures of the eye.					

Infections and infestations					
	Grade				
Adverse Event	1	2	3	4	5
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: A disorder characterized by an infectious process involving the small and large intestines.					
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 characterized by an infectious process involving 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 characterized by an infectious process involving 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 characterized by an infectious process involving 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 characterized by an infectious process involving 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 characterized by an infectious process involving the liver.					
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 characterized by a viral pathologic process involving 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 characterized by an infectious process involving 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 characterized by an infectious process involving a joint.					
Kidney infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the kidney.					

Infections and infestations					
	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 characterized 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 characterized by an infectious process involving 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 characterized by an infectious process involving 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 characterized by an infectious process involving the lymph nodes.					
Mediastinal infection	-	-	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 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 characterized 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 characterized by an infectious process involving 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 characterized by an infectious process involving 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
Definition: A disorder characterized by an infectious process involving the outer ear and ear canal. Contributory factors include excessive water exposure (swimmer's ear infection) and cuts in the ear canal. Symptoms include fullness, itching, swelling and marked discomfort in the ear and ear drainage.					
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 characterized by an infectious process involving 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 intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the ovary.					

Infections and infestations					
	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 characterized by an infectious process involving 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; life-threatening consequences	Death
Definition: A disorder characterized by an eruption consisting of papules (a small, raised pimple) and pustules (a small pus filled blister), typically appearing in face, scalp, and upper chest and back Unlike acne, this rash does not present with whiteheads or blackheads, and can be symptomatic, with itchy or tender lesions.					
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 characterized by an infectious process involving the soft tissues around the nail.					
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 characterized by an infectious process involving the pelvic cavity.					
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 characterized by an infectious process involving 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
Definition: A disorder characterized by an infectious process involving the orbit of the eye.					
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
Definition: A disorder characterized by an infectious process involving the peripheral nerves.					
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 characterized by an infectious process involving the peritoneum.					
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 characterized 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 characterized by an infectious process involving the vein. Clinical manifestations include erythema, marked discomfort, swelling, and induration along the course of the infected vein.					
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 characterized by an infectious process involving 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 characterized by an infectious process involving 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 characterized by a circumscribed and elevated skin lesion filled with pus.					
Rhinitis 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	-	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 characterized by an infectious process involving 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 characterized by an infectious process involving the scrotum.					
Sepsis	-	-	-	Life-threatening consequences; urgent intervention indicated	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 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 characterized by an infectious process involving 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
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	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the small intestine.					
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 characterized by an infectious process involving soft tissues.					
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				
Adverse Event	1	2	3	4	5
Definition: A disorder characterized by an infectious process involving the spleen.					
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 characterized by an infectious process involving a stoma (surgically created opening 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 characterized by an infectious process involving 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 characterized by an infectious process involving the trachea.					
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 characterized by an infectious process involving the upper respiratory tract (nose, paranasal sinuses, pharynx, larynx, 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 characterized by an infectious process involving 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 characterized by an infectious process involving the urinary tract, most commonly 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 characterized by an infectious process involving the endometrium. It may extend to the myometrium and parametrial 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 characterized by an infectious process involving 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 characterized by an infectious process involving 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 characterized by an infectious process involving the wound.					
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 indicated	Limiting instrumental ADL; operative intervention indicated	Limiting self care ADL; elective surgery indicated	-	-
Definition: A finding of damage to the ankle joint characterized by a break in the continuity of the ankle bone. Symptoms include marked discomfort, swelling and difficulty moving the affected leg and foot.					
Aortic injury	-	-	Severe symptoms; limiting self care ADL; disabling; repair or revision indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to the aorta.					
Arterial injury	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); repair or revision not indicated	Severe symptoms; limiting self care ADL; disabling; repair or revision indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to an artery.					
Biliary 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 bile due to breakdown of a biliary anastomosis (surgical connection of two separate anatomic structures).					
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 of urine due to breakdown of a bladder anastomosis (surgical connection of two separate anatomic structures).					
Bruising	Localized or in a dependent area	Generalized	-	-	-
Definition: A finding of injury of the soft tissues or bone characterized by leakage of blood into surrounding tissues.					
Burn	Minimal symptoms; intervention not indicated	Medical intervention; minimal debridement indicated	Moderate to major debridement or reconstruction indicated	Life-threatening consequences	Death
Definition: A finding of impaired integrity to the anatomic site of an adverse thermal reaction. Burns can be caused by exposure to chemicals, direct heat, electricity, flames and radiation. The extent of damage depends on the length and intensity of exposure and time until provision of treatment.					
Dermatitis radiation	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 cutaneous inflammatory reaction occurring as a result of exposure to biologically effective levels of ionizing radiation.					
Esophageal 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 due to breakdown of an esophageal anastomosis (surgical connection of two separate anatomic structures).					
Fall	Minor with no resultant injuries; intervention not indicated	Symptomatic; noninvasive intervention indicated	Hospitalization indicated	-	-
Definition: A finding of sudden movement downward, usually resulting in injury.					
Fallopian tube anastomotic leak	Asymptomatic; clinical or 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 due to breakdown of a fallopian tube anastomosis (surgical connection of two separate anatomic structures).					
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 diagnostic observations only; intervention not indicated	Symptomatic but non-displaced; immobilization indicated	Severe symptoms; displaced or open wound with bone exposure; disabling; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of traumatic injury to the bone in which the continuity of the bone is broken.					

Injury, poisoning and procedural complications					
	Grade				
Adverse Event	1	2	3	4	5
Gastric 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 due to breakdown of a gastric anastomosis (surgical connection of two separate anatomic structures).					
Gastrointestinal 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 due to breakdown of a gastrointestinal anastomosis (surgical connection of two separate anatomic structures).					
Gastrointestinal stoma necrosis	-	Superficial necrosis; intervention not indicated	Severe symptoms; hospitalization or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of a necrotic process occurring in the gastrointestinal tract stoma.					
Hip fracture	-	Hairline fracture; mild pain; limiting instrumental ADL; non-surgical intervention indicated	Severe pain; hospitalization or intervention indicated for pain control (e.g., traction); operative intervention indicated	Life-threatening consequences; symptoms associated with neurovascular compromise	-
Definition: A finding of traumatic injury to the hip in which the continuity of either the femoral head, femoral neck, intertrochanteric or subtrochanteric regions is broken.					
Injury to carotid artery	-	-	Severe symptoms; limiting self care ADL (e.g., transient cerebral ischemia); repair or revision indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the carotid artery.					
Injury to inferior vena cava	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the inferior vena cava.					
Injury to jugular vein	-	-	Symptomatic limiting self care ADL; disabling; repair or revision indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the jugular vein.					
Injury to superior vena cava	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; repair or revision not indicated	Severe symptoms; limiting self care ADL; disabling; repair or revision indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to the superior vena cava.					
Intestinal stoma 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 contents from an intestinal stoma (surgically created opening on the surface of the body).					
Intestinal stoma obstruction	-	Self-limited; intervention not indicated	Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of blockage of the normal flow of the contents of the intestinal stoma.					
Intestinal stoma 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 leakage from the intestinal stoma.					
Intraoperative arterial 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 an artery during a surgical procedure.					
Intraoperative breast 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

Injury, poisoning and procedural complications					
	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
Definition: A finding of damage to the heart during a surgical procedure.					
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
Definition: A finding of damage to the ear during a surgical procedure.					
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 surgical 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 during 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 surgical procedure.					
Intraoperative hemorrhage	-	-	Postoperative radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of uncontrolled bleeding during a surgical procedure.					
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 biliary tract during a surgical procedure.					
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 the musculoskeletal system during a surgical procedure.					
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
Definition: A finding of damage to the nervous system during a surgical procedure.					
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 procedure.					
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 procedure.					
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; disabling	Life-threatening consequences; urgent intervention indicated	Death

Injury, poisoning and procedural complications					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A finding of damage to the reproductive organs during a surgical procedure.					
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 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 procedure.					
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 the spleen during a surgical procedure.					
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 the urinary system during a surgical procedure.					
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 a vein during a surgical procedure.					
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 kidney anastomosis (surgical connection of two separate anatomic structures).					
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 due to breakdown of an anastomosis (surgical connection of two separate anatomic structures) in the large 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 due to breakdown of a pancreatic anastomosis (surgical connection of two separate anatomic structures).					
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 due to breakdown of a pharyngeal anastomosis (surgical connection of two separate anatomic structures).					
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 occurring after a surgical procedure.					
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 previously undocumented problem that occurs after a thoracic procedure.					
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 surface.					
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 displacement 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 chemotherapeutic agents, for weeks or months following radiotherapy. The inflammatory reaction is confined to the previously irradiated skin and the symptoms disappear after the removal of the pharmaceutical agent.					
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 due to breakdown of a rectal anastomosis (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.					
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 due to breakdown of an anastomosis (surgical connection of two separate anatomic structures) in the small 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 due to breakdown of a spermatic cord anastomosis (surgical connection of two separate anatomic structures).					
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 continuity of a vertebral bone is broken.					
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 (surgically created opening on the surface of the body).					
Stomal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the jejunal mucosal surface close to the anastomosis site following a gastroenterostomy procedure.					
Tracheal hemorrhage	Minimal bleeding identified on clinical or diagnostic 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 trachea.					
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
Definition: A finding of blockage of the lumen of the trachea.					

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 leakage 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
Definition: A finding of leakage due to breakdown of a ureteral anastomosis (surgical connection of two separate anatomic structures).					
Urethral 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 due to breakdown of a urethral anastomosis (surgical connection of two 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 contents from a urostomy.					
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 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 due to breakdown of a uterine anastomosis (surgical connection of two 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
Definition: A disorder characterized by a rupture in the uterine wall.					
Vaginal 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 due to breakdown of a vaginal anastomosis (surgical connection of two separate anatomic structures).					
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 due to breakdown of a vas deferens anastomosis (surgical connection of two separate anatomic structures).					
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
Definition: A finding of a previously undocumented problem related to the vascular access site.					

Injury, poisoning and procedural 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
Definition: A finding of development of a new problem at the site of an existing wound.					
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 dehiscence 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.					
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 broken.					
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	-	-
Definition: An abnormal laboratory test result in which the partial thromboplastin time is found to be greater than the control value. As a possible indicator of coagulopathy, a prolonged partial thromboplastin time (PTT) may occur in a variety of diseases and disorders, both primary and related to treatment.					
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 laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in 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 laboratory test results that indicate an increase in the level of alkaline phosphatase 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 laboratory test results that indicate an 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 laboratory test results that indicate abnormal levels of antidiuretic hormone 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 laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated 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 laboratory test results that indicate an decrease in levels of corticotrophin 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 laboratory test results that indicate abnormal levels of gonadotrophin hormone 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 laboratory test results that indicate abnormal levels of prolactin hormone 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 lung 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 which indicates increased levels of cardiac troponin I in a biological specimen.					
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 biological specimen.					
CD4 lymphocytes decreased	<LLN - 500/mm3; <LLN - 0.5 x 10e9 /L	<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 laboratory test results that indicate an decrease in levels of CD4 lymphocytes 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 laboratory test results that indicate higher than normal levels of cholesterol 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 laboratory test results that indicate an increase in levels of creatine phosphokinase 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 laboratory test results that indicate increased levels of creatinine in a biological 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 computed when the amount of blood ejected during a ventricular contraction of the heart is compared to the amount that was present prior to the contraction.					
Electrocardiogram QT corrected interval prolonged	QTc 450 - 480 ms	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 dysrhythmia characterized by an abnormally long corrected QT interval.					
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 laboratory test results that indicate an decrease in levels of fibrinogen 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 test results that indicate a relative decrease 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 laboratory test results that indicate higher than normal levels of the enzyme gamma-glutamyltransferase in the blood specimen. GGT (gamma-glutamyltransferase) catalyzes the transfer of a gamma glutamyl group from a gamma glutamyl peptide to another peptide, amino acids 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 laboratory test results that indicate abnormal levels of growth hormone in a biological specimen.					
Haptoglobin decreased	<LLN	-	-	-	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of haptoglobin 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 laboratory test results that indicate increased 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 laboratory test results that indicate an increase in the ratio of the patient's prothrombin time to a control sample 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 laboratory test results that indicate an increase in the level of lipase in a biological specimen.					
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9 /L	<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 laboratory test results that indicate a decrease in number of lymphocytes in a blood specimen.					
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	-
Definition: A finding based on laboratory test results that indicate an abnormal increase in the number of lymphocytes in the blood, effusions or bone marrow.					
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<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 laboratory test results that indicate a decrease in number of neutrophils in a blood specimen.					
Pancreatic enzymes decreased	<LLN and asymptomatic	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency	-	-
Definition: A finding based on laboratory test results that indicate an 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/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-
Definition: A finding based on laboratory 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 laboratory test results that indicate an 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 test results that indicate urine production is less relative to previous output.					
Vital capacity abnormal	90 - 75% of predicted value	<75 - 50% of predicted value; limiting instrumental ADL	<50% of predicted value; limiting self care ADL	-	-
Definition: A finding based on pulmonary function test results that indicate an abnormal vital capacity (amount of exhaled after a maximum inhalation) when compared to the predicted value.					
Weight gain	5 - <10% from baseline	10 - <20% from baseline	>=20% from baseline	-	-
Definition: A finding characterized by an increase in overall body weight; for pediatrics, greater than the baseline growth curve.					
Weight loss	5 to <10% from baseline; intervention not indicated	10 - <20% from baseline; nutritional support indicated	>=20% from baseline; tube feeding or TPN indicated	-	-
Definition: A finding characterized by a decrease in overall body weight; for pediatrics, less than the baseline growth curve.					
White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate an decrease in number of white blood cells in a blood specimen.					
Investigations - 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

Metabolism and nutrition disorders					
	Grade				
Adverse Event	1	2	3	4	5
Acidosis	pH <normal, but >=7.3	-	pH <7.3	Life-threatening consequences	Death
Definition: A disorder characterized by abnormally high acidity (high hydrogen-ion concentration) of the blood and other body tissues.					
Alcohol intolerance	-	Present	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in sensitivity to the adverse effects of alcohol, which can include nasal congestion, skin flushes, heart dysrhythmias, nausea, vomiting, indigestion and headaches.					
Alkalosis	pH >normal, but <=7.5	-	pH >7.5	Life-threatening consequences	Death
Definition: A disorder characterized by abnormally high alkalinity (low hydrogen-ion concentration) of the blood and other body tissues.					
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 characterized 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 characterized by excessive loss of water from the body. It is usually caused by severe diarrhea, vomiting or diaphoresis.					
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 characterized by an inability to properly metabolize 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; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of calcium (corrected for albumin) 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 characterized by laboratory test results that indicate an elevation in the concentration of blood sugar. It is usually an indication of diabetes mellitus or glucose intolerance.					
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 characterized by laboratory test results that indicate an elevation in the concentration of potassium in the blood; associated with kidney failure or sometimes with the use of diuretic drugs.					
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 characterized by laboratory test results that indicate an elevation in the concentration of magnesium in the blood.					
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of sodium in the blood.					
Hypertriglyceridemia	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
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of triglyceride concentration in the blood.					
Hyperuricemia	>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
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of uric acid.					
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of albumin in the blood.					

Metabolism and nutrition disorders					
	Grade				
Adverse Event	1	2	3	4	5
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized 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 characterized by laboratory test results that indicate a low concentration of calcium (corrected for albumin) in the blood.					
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<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 characterized by laboratory test results that indicate a low concentration of glucose in the blood.					
Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of potassium in the blood.					
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<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 characterized by laboratory test results that indicate a low concentration of magnesium in the blood.					
Hyponatremia	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of sodium in the blood.					
Hypophosphatemia	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<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 characterized by laboratory test results that indicate a low concentration of phosphates in the blood.					
Iron overload	-	Moderate symptoms; intervention not indicated	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by accumulation of iron in the tissues.					
Obesity	-	BMI 25 - 29.9 kg/m2	BMI 30 - 39.9 kg/m2	BMI >=40 kg/m2	-
Definition: A disorder characterized by having a high amount of body fat.					
Tumor lysis syndrome	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by metabolic abnormalities that result from a spontaneous or therapy-related cytolysis of tumor cells.					
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				
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 characterized by a necrotic process occurring in the soft tissues of the abdominal wall.					
Arthralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in a joint.					
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 characterized by inflammation involving a joint.					
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
Definition: A disorder characterized by necrotic changes in the bone tissue due to interruption of blood supply. Most often affecting the epiphysis of the long bones, the necrotic changes result in the collapse and the destruction of the bone structure.					
Back pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the back region.					
Bone pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the bones.					
Buttock pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the buttocks.					
Chest wall pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation 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 characterized 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 characterized 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 characterized by marked discomfort sensation on the lateral side of the body in the region below the ribs and above 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 characterized by a reduction in the strength of muscles in multiple anatomic sites.					
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	-	-
Definition: A disorder characterized by of stature that is smaller than normal as expected for age.					

Musculoskeletal and connective tissue disorders					
	Grade				
Adverse Event	1	2	3	4	5
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 characterized 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 characterized by excessive fluid in a joint, usually as a result of joint inflammation.					
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 characterized 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 characterized by a decrease in flexibility of a cervical spine joint.					
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 characterized 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 characterized by an abnormal increase in the curvature of the thoracic portion 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 characterized 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 characterized by a reduction in the strength of the muscles on the left side of the 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 characterized by a reduction in the strength of 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 characterized by a reduction in the strength of the muscles on the right side of the body.					
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	-	-
Definition: A disorder characterized by a reduction in the strength of the trunk muscles.					
Muscle weakness upper 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 characterized by a reduction in the strength of the upper limb muscles.					

Musculoskeletal and connective tissue disorders					
	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 characterized by of a malformation of the musculoskeletal system.					
Myalgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation originating from a muscle or group 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 characterized by inflammation involving the skeletal muscles.					
Neck pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the neck area.					
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 characterized 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 characterized 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 characterized by reduced bone mass, with a decrease in cortical thickness and in the number and size of the trabeculae of cancellous bone (but normal chemical composition), resulting in increased fracture incidence.					
Pain in extremity	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the upper or lower extremities.					
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
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the pelvis.					
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 characterized by a malformed, lateral curvature 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 characterized by a necrotic process occurring in the soft tissues of the lower extremity.					
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
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the upper extremity.					

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 characterized 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 characterized by lack of ability to open the mouth 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	Severe length discrepancy >5 cm; limiting self care ADL; disabling; operative intervention indicated	-	-
Definition: A disorder characterized by of a discrepancy between the lengths of the lower or upper extremities.					
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 benign, malignant and unspecified (incl cysts and polyps)					
	Grade				
Adverse Event	1	2	3	4	5
Leukemia secondary to oncology chemotherapy	-	-	-	Present	Death
Definition: A disorder characterized by leukemia arising as a result of the mutagenic effect of chemotherapy agents.					
Myelodysplastic syndrome	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by insufficiently healthy hematapoietic cell production by the bone marrow.					
Treatment related secondary malignancy	-	-	Non life-threatening secondary malignancy	Acute life-threatening secondary malignancy; blast crisis in leukemia	Death
Definition: A disorder characterized by development of a malignancy most probably as a result of treatment for a previously existing malignancy.					
Tumor pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort from a neoplasm that may be pressing on a nerve, blocking blood vessels, inflamed or fractured from metastasis.					
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					
	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 characterized by involvement of the abducens nerve (sixth cranial nerve).					
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 characterized by involvement of the accessory 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 characterized by involvement of the acoustic nerve (eighth cranial nerve).					
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 characterized by an uncomfortable feeling of inner restlessness and inability to stay still; this is a side effect of some psychotropic drugs.					
Amnesia	Mild; transient memory loss	Moderate; short term memory loss; limiting instrumental ADL	Severe; long term memory loss; limiting self care ADL	-	-
Definition: A disorder characterized by systematic and extensive loss of memory.					
Aphonia	-	-	Voicelessness; unable to speak	-	-
Definition: A disorder characterized by the inability to speak. It may result from injuries to the vocal cords or may be functional (psychogenic).					
Arachnoiditis	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the arachnoid membrane and adjacent subarachnoid space.					
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 characterized by lack of coordination of muscle movements resulting in the impairment or inability to perform voluntary 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 characterized by regional paresthesia of the brachial plexus, marked discomfort and muscle weakness, and limited 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 characterized by a necrotic process occurring 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 characterized by loss of cerebrospinal fluid into 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 characterized by a conspicuous change in cognitive 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	-	-
Definition: A disorder characterized by a deterioration in the ability to concentrate.					

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 characterized by a decrease in ability to perceive and respond.					
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 characterized by a disturbing sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking.					
Dysarthria	Mild slurred speech	Moderate impairment of articulation or slurred speech	Severe impairment of articulation or slurred speech	-	-
Definition: A disorder characterized by slow and slurred speech resulting from an inability to coordinate 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 characterized by distortion of sensory perception, 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 characterized by abnormal sensual experience with the taste of foodstuffs; it can 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 characterized by impairment of verbal communication skills, often resulting from brain damage.					
Edema cerebral	-	-	-	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the brain.					
Encephalopathy	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a pathologic process involving the brain.					
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 characterized by abnormal, repetitive, involuntary muscle movements, frenzied speech and extreme restlessness.					
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 characterized by a reduction in the strength 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 characterized by involvement of the facial nerve (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 characterized by involvement of the glossopharyngeal nerve (ninth cranial nerve).					
Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in various parts of the head, not confined to the area of distribution 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 characterized by an abnormal increase of cerebrospinal fluid in the ventricles of the brain.					
Hypersomnia	Mild increased need for sleep	Moderate increased need for sleep	Severe increased need for sleep	-	-
Definition: A disorder characterized 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 diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the hypoglossal 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 characterized by bleeding from the cranium.					
Ischemia cerebrovascular	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	-	-	-
Definition: A disorder characterized by a decrease or absence of blood supply to the brain caused by obstruction (thrombosis or embolism) of an artery resulting in neurological damage.					
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 characterized by involvement of the trochlear nerve (fourth cranial nerve).					
Lethargy	Mild symptoms; reduced alertness and awareness	Moderate symptoms; limiting instrumental ADL	-	-	-
Definition: A disorder characterized by a decrease in consciousness characterized by mental and physical 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 characterized by diffuse reactive astrocytosis with multiple areas of necrotic foci without inflammation.					
Memory impairment	Mild memory impairment	Moderate memory impairment; limiting instrumental ADL	Severe memory impairment; limiting self care ADL	-	-
Definition: A disorder characterized by a deterioration in memory function.					
Meningismus	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by neck stiffness, headache, and photophobia resulting from irritation of the cerebral meninges.					
Movements involuntary	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by uncontrolled and purposeless movements.					
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 characterized by inflammation involving the spinal cord. Symptoms include weakness, paresthesia, sensory loss, marked discomfort and incontinence.					
Neuralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by intense painful sensation along a nerve or group of nerves.					
Nystagmus	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involuntary movements of the eyeballs.					
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 characterized by involvement of the oculomotor nerve (third cranial nerve).					
Olfactory nerve disorder	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the olfactory nerve (first cranial nerve).					

Nervous system disorders					
	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 characterized by functional disturbances of sensory neurons resulting in abnormal cutaneous sensations of tingling, numbness, pressure, cold, and warmth that are experienced in the absence of a stimulus.					
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 characterized by inflammation or degeneration 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 characterized by inflammation or degeneration of the peripheral sensory nerves.					
Phantom pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort related to a limb or an organ that is removed from or is not physically part of the body.					
Presyncope	-	Present (e.g., near fainting)	-	-	-
Definition: A disorder characterized by an episode of lightheadedness and dizziness which may precede an episode of syncope.					
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
Definition: A disorder characterized by dysfunction of the corticospinal (pyramidal) tracts of the spinal cord. Symptoms include an increase in the muscle tone in the lower extremities, hyperreflexia, positive Babinski and a decrease in fine motor coordination.					
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 characterized by inflammation involving a nerve root. Patients experience marked discomfort radiating along a nerve path because of spinal pressure on the connecting nerve root.					
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 characterized by paralysis of the recurrent laryngeal 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
Definition: A disorder characterized by headaches, mental status changes, visual disturbances, and seizures associated with imaging findings of posterior leukoencephalopathy. It has been observed in association with hypertensive encephalopathy, eclampsia, and immunosuppressive and cytotoxic drug treatment. It is an acute or subacute reversible condition.					
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 characterized by a sudden, involuntary skeletal muscular contractions of cerebral or brain stem origin.					
Sinus pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort in the face, between the eyes, or upper teeth 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 characterized 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 by increased involuntary muscle tone that affects the regions interfering with voluntary movement. It results in gait, movement, and speech disturbances.					
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 characterized by a sudden loss of sensory function due to an intracranial vascular event.					
Syncope	-	-	Fainting; orthostatic collapse	-	-
Definition: A disorder characterized by spontaneous loss of consciousness caused by insufficient blood supply to the brain.					

Nervous system disorders					
	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 characterized by a brief attack (less than 24 hours) of cerebral dysfunction of vascular origin, with no persistent neurological deficit.					
Tremor	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by the uncontrolled shaking movement of the whole body or individual 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 characterized by involvement of the trigeminal 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 characterized by involvement of the vagus nerve (tenth cranial nerve).					
Vasovagal reaction	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a sudden drop of the blood pressure, bradycardia, and peripheral vasodilation that may lead to loss of consciousness. It results from an increase in the stimulation of the vagus nerve.					
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

Pregnancy, puerperium and perinatal conditions					
	Grade				
Adverse Event	1	2	3	4	5
Fetal death	-	-	-	-	Fetal loss at any gestational age
Definition: A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without 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 characterized by inhibition of fetal growth resulting 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 characterized by delivery of a viable infant before the normal end of gestation. Typically, viability is achievable between the twentieth and thirty-seventh week of gestation.					
Unintended pregnancy	-	-	Unintended pregnancy	-	-
Definition: A disorder characterized by an unexpected pregnancy at 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; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Psychiatric disorders					
	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
Definition: A disorder characterized by a state of restlessness associated with unpleasant feelings of irritability and tension.					
Anorgasmia	Inability to achieve orgasm not adversely affecting relationship	Inability to achieve orgasm adversely affecting relationship	-	-	-
Definition: A disorder characterized by an inability to achieve orgasm.					
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 characterized by apprehension of danger and dread accompanied by restlessness, tension, tachycardia, and dyspnea unattached to a clearly identifiable stimulus.					
Confusion	Mild disorientation	Moderate disorientation; limiting instrumental ADL	Severe disorientation; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a lack of clear and orderly thought and behavior.					
Delayed orgasm	Delay in achieving orgasm not adversely affecting relationship	Delay in achieving orgasm adversely affecting relationship	-	-	-
Definition: A disorder characterized by sexual dysfunction characterized by a delay in climax.					
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 characterized by the acute and sudden development of confusion, illusions, movement changes, inattentiveness, agitation, and hallucinations. Usually, it is a reversible condition.					
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 characterized by false personal beliefs held contrary to reality, despite contradictory evidence and common sense.					
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 characterized by melancholic feelings of grief or unhappiness.					
Euphoria	Mild mood elevation	Moderate mood elevation	Severe mood elevation (e.g., hypomania)	-	-
Definition: A disorder characterized by an exaggerated feeling of well-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 characterized by a false sensory perception in the absence of an external stimulus.					
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 characterized by difficulty in falling asleep and/or remaining asleep.					
Libido decreased	Decrease in sexual interest not adversely affecting relationship	Decrease in sexual interest adversely affecting relationship	-	-	-
Definition: A disorder characterized 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 characterized 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 characterized by excitement of psychotic proportions manifested by mental and physical hyperactivity, disorganization 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 disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A disorder characterized by a conspicuous change in a 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 characterized by personality change, impaired functioning, and loss of touch with reality. It may be a manifestation of schizophrenia, bipolar disorder or brain tumor.					
Restlessness	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by an inability to rest, relax or be 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 characterized by thoughts of taking one's own 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 characterized by self-inflicted harm in an attempt 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	Creatinine 2 - 3 x above baseline	Creatinine >3 x baseline or >4.0 mg/dL; hospitalization indicated	Life-threatening consequences; dialysis indicated	Death
Definition: A disorder characterized by the acute loss of renal function and is traditionally classified as pre-renal (low blood flow into kidney), renal (kidney damage) and post-renal causes (ureteral or bladder outflow obstruction).					
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 characterized by a rupture in the bladder wall.					
Bladder spasm	Intervention not indicated	Antispasmodics indicated	Hospitalization indicated	-	-
Definition: A disorder characterized by a sudden and involuntary contraction of the bladder wall.					
Chronic kidney disease	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN - 60 ml/min/1.73 m2 or proteinuria 2+ present; urine protein/creatinine >0.5	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 characterized by gradual and usually permanent loss of kidney function resulting 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 characterized by inflammation of the bladder which is not caused by an infection 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 characterized by laboratory test results that indicate blood in the urine.					
Hemoglobinuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characterized by laboratory test results that indicate the presence of free hemoglobin 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 characterized by laboratory test results that indicate the presence of excessive protein in the urine. It is predominantly 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 characterized by the formation of crystals in the 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	-	-
Definition: A disorder characterized by paroxysmal and severe flank marked discomfort radiating to the inguinal area. Often, the cause is the passage of kidney stones.					

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 characterized 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 characterized by an abnormal communication between any part of the urinary system and another organ or anatomic site.					
Urinary frequency	Present	Limiting instrumental ADL; medical management indicated	-	-	-
Definition: A disorder characterized by urination at short intervals.					
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 characterized by inability to control the flow of 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 characterized by accumulation of urine within the bladder because of the inability 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 characterized 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 characterized by a sensation of marked discomfort in the urinary tract.					
Urinary urgency	Present	Limiting instrumental ADL; medical management indicated	-	-	-
Definition: A disorder characterized by a sudden compelling urge to urinate.					
Urine discoloration	Present	-	-	-	-
Definition: A disorder characterized 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

Reproductive system and breast disorders					
	Grade				
Adverse Event	1	2	3	4	5
Azoospermia	-	-	Absence of sperm in ejaculate	-	-
Definition: A disorder characterized by laboratory test results that indicate complete absence of spermatozoa in the semen.					
Breast atrophy	Minimal asymmetry; minimal atrophy	Moderate asymmetry; moderate atrophy	Asymmetry >1/3 of breast volume; severe atrophy	-	-
Definition: A disorder characterized by underdevelopment of the breast.					
Breast pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the breast region.					
Dysmenorrhea	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by abnormally painful abdominal cramps during menses.					
Dyspareunia	Mild discomfort or pain associated with vaginal penetration; discomfort relieved with use of vaginal lubricants or estrogen	Moderate discomfort or pain associated with vaginal penetration; discomfort or pain partially relieved with use of vaginal lubricants or estrogen	Severe discomfort or pain associated with vaginal penetration; discomfort or pain unrelieved by vaginal lubricants or estrogen	-	-
Definition: A disorder characterized by painful or difficult coitus.					
Ejaculation disorder	Diminished ejaculation	Anejaculation or retrograde ejaculation	-	-	-
Definition: A disorder characterized by problems related to ejaculation. This category includes premature, delayed, retrograde and painful ejaculation.					
Erectile dysfunction	Decrease in erectile function (frequency or rigidity of erections) but intervention not indicated (e.g., medication or use of mechanical device, penile pump)	Decrease in erectile function (frequency/rigidity of erections), erectile intervention indicated, (e.g., medication or mechanical devices such as penile pump)	Decrease in erectile function (frequency/rigidity of erections) but erectile intervention not helpful (e.g., medication or mechanical devices such as penile pump); placement of a permanent penile prosthesis indicated (not previously present)	-	-
Definition: A disorder characterized by the persistent or recurrent inability to achieve or to maintain an erection during sexual activity.					
Fallopian tube obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by blockage of the normal flow of the contents in the fallopian tube.					
Fallopian tube stenosis	Asymptomatic clinical or 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 disorder characterized by a narrowing of the fallopian tube lumen.					
Female genital tract 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 characterized by an abnormal communication between a female reproductive system organ and another organ or anatomic site.					
Feminization acquired	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by the development of secondary female sex characteristics in males due to extrinsic factors.					
Genital edema	Mild 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	Lymphorrhea; gross deviation from normal anatomic contour; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the genitals.					
Gynecomastia	Asymptomatic breast enlargement	Symptomatic (e.g., pain or psychosocial impact)	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by excessive development of the breasts in males.					
Hematosalpinx	Minimal bleeding identified on imaging study or laparoscopy; 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

Reproductive system and breast disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A disorder characterized by the presence of blood in a fallopian tube.					
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 characterized by irregular cycle or duration of menses.					
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 characterized by disturbances of milk secretion. It is not necessarily related to pregnancy that is observed in females and can be observed in males.					
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 characterized by abnormally heavy vaginal bleeding 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 characterized 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 characterized 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 characterized 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 characterized by tearing or disruption of the ovarian tissue.					
Ovulation pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in one side of the abdomen between menstrual cycles, around the time of the discharge of the ovum from the ovarian follicle.					
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 characterized by a reduction in the strength of the muscles of the pelvic floor.					
Pelvic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the pelvis.					
Penile pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the penis.					
Perineal 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 area between the genital organs and the anus.					
Premature menopause	-	-	Present	-	-
Definition: A disorder characterized by ovarian failure before the age of 40. Symptoms include hot flashes, 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

Reproductive system and breast disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A disorder characterized by bleeding from the prostate gland.					
Prostatic obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by compression of the urethra secondary to enlargement of the prostate gland. This results in voiding difficulties (straining to void, slow urine stream, and incomplete emptying of the bladder).					
Prostatic 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 prostate gland.					
Scrotal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation 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 characterized 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 characterized by blockage of the normal flow of the contents of the spermatic cord.					
Testicular disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic but not interfering with urination or sexual activities; intervention not indicated; limiting instrumental ADL	Severe symptoms; interfering with urination or sexual function; limiting self care ADL; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by involvement of the testis.					
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 characterized by bleeding from the testis.					
Testicular 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 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 characterized by an abnormal communication 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 characterized 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 characterized by blockage of the uterine outlet.					
Uterine 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 uterus.					
Vaginal discharge	Mild vaginal discharge (greater than baseline for patient)	Moderate to heavy vaginal discharge; use of perineal pad or tampon indicated	-	-	-
Definition: A disorder characterized by vaginal secretions. Mucus produced by the cervical glands is discharged from the vagina naturally, especially during the childbearing years.					
Vaginal dryness	Mild vaginal dryness not interfering with sexual function	Moderate vaginal dryness interfering with sexual function or causing frequent discomfort	Severe vaginal dryness resulting in dyspareunia or severe discomfort	-	-
Definition: A disorder characterized by an uncomfortable feeling of itching and burning in the vagina.					

Reproductive system and breast 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 characterized 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 characterized 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 characterized by inflammation involving the vagina. Symptoms may include redness, edema, marked discomfort and an increase in vaginal discharge.					
Vaginal obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by blockage of vaginal canal.					
Vaginal 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 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 characterized 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 characterized by a narrowing of the vaginal canal.					
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 characterized by involuntary spasms of the pelvic floor muscles, resulting in pathologic tightness of the vaginal wall during penetration such as during sexual intercourse.					
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

Respiratory, thoracic and mediastinal 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 characterized by progressive and life-threatening pulmonary distress in the absence of an underlying pulmonary condition, usually following major trauma or surgery.					
Allergic rhinitis	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by an inflammation of the nasal mucous membranes caused by an IgE-mediated response to external allergens. The inflammation may also involve the mucous membranes of the sinuses, eyes, middle ear, and pharynx. Symptoms include sneezing, nasal congestion, rhinorrhea and itching.					
Apnea	-	-	Present; medical intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by cessation of breathing.					
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 characterized by inhalation of solids or liquids into the lungs.					
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 characterized by the collapse of part or the entire lung.					
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 characterized by an abnormal communication between the bronchus and another 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 characterized by blockage of a bronchus passage, most often by bronchial secretions 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
Definition: A disorder characterized by a narrowing of the bronchial tube.					
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 characterized by an abnormal communication between a bronchus and the pleural cavity.					
Bronchopulmonary 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 characterized by bleeding from the bronchial wall and/or lung parenchyma.					

Respiratory, thoracic and mediastinal disorders					
	Grade				
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 characterized by a sudden contraction of the smooth muscles of the bronchial wall.					
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 characterized by milky pleural effusion (abnormal collection of fluid) resulting from 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 characterized by sudden, often repetitive, spasmodic contraction of the thoracic cavity, resulting in violent release of air from the lungs and usually accompanied by a distinctive sound.					
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 characterized 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 characterized 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 characterized by repeated gulp sounds that result from an involuntary opening and closing of the glottis. This is attributed to a spasm of the diaphragm.					
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 characterized by harsh and raspy voice arising 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
Definition: A disorder characterized by a decrease in the level of oxygen in the body.					
Laryngeal 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
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the larynx.					
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 characterized 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 characterized by bleeding from the larynx.					
Laryngeal inflammation	Mild sore throat; raspy voice	Moderate sore throat; analgesics indicated	Severe throat pain; endoscopic intervention indicated	-	-
Definition: A disorder characterized by an inflammation involving the larynx.					

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 characterized by an inflammation involving the mucous membrane of the larynx.					
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 characterized by blockage of the laryngeal airway.					
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
Definition: A disorder characterized by a narrowing of the laryngeal airway.					
Laryngopharyngeal dysesthesia	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 characterized by an uncomfortable persistent sensation in the area of the laryngopharynx.					
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 characterized by paroxysmal spasmodic muscular contraction of the vocal cords.					
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 characterized by bleeding from the mediastinum.					
Nasal congestion	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Associated with bloody nasal discharge or epistaxis	-	-
Definition: A disorder characterized by obstruction of the nasal passage due to mucosal edema.					
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 characterized by an abnormal communication between the pharynx and another organ or anatomic site.					
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 characterized by bleeding from the pharynx.					
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 characterized by an inflammation involving the mucous membrane of the pharynx.					
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 characterized 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 characterized by a narrowing of the pharyngeal airway.					
Pharyngolaryngeal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation 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	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by an increase in amounts of fluid within the pleural cavity. Symptoms include shortness of breath, cough and marked chest discomfort.					
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 characterized by bleeding from the pleural cavity.					
Pleuritic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the pleura.					
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
Definition: A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma.					
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 characterized 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 characterized by excessive mucous secretion in the back of the nasal cavity or throat, causing sore throat and/or coughing.					
Productive cough	Occasional/minimal production of sputum with cough	Moderate sputum production; limiting instrumental ADL	Persistent or copious production of sputum; limiting self care ADL	-	-
Definition: A disorder characterized by expectorated secretions upon coughing.					
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 characterized by accumulation of fluid in the lung tissues that causes a disturbance 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 characterized by the replacement of the lung tissue by connective tissue, leading to progressive dyspnea, respiratory 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

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Definition: A disorder characterized by an abnormal communication between the lung and another organ 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 characterized by an increase in pressure within 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 characterized by impaired gas exchange by the respiratory system resulting in hypoxemia and a decrease in oxygenation of the tissues that may be associated with an increase in arterial levels of carbon dioxide.					
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 characterized by weight gain, dyspnea, pleural and pericardial effusions, leukocytosis and/or renal failure originally described in patients treated with all-trans retinoic acid.					
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 characterized by involvement of the paranasal 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 characterized by cessation of breathing for short periods during sleep.					
Sneezing	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized 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 characterized 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 characterized by a high pitched breathing sound due to laryngeal or upper airway 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 characterized by an abnormal communication between the trachea and another 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
Definition: A disorder characterized by an inflammation involving the mucous membrane of the trachea.					
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 characterized by a narrowing of the trachea.					

Respiratory, thoracic and mediastinal 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 characterized by a change in the sound and/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 characterized by a high-pitched, whistling sound during breathing. It results from the narrowing or obstruction of the 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 cover the hair loss but it does not require a wig or hair piece to camouflage	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; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by a decrease in density of hair compared to normal for a given individual 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 characterized by an abnormal body smell resulting from the growth of bacteria on the body.					
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 characterized by inflammation of the skin characterized by the presence of bullae which are filled with fluid.					
Dry 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 characterized 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 characterized by target lesions (a pink-red ring around a pale center).					
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 characterized by generalized inflammatory erythema and exfoliation. The inflammatory process involves > 90% of 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	-	-
Definition: A disorder characterized by shrinking of adipose tissue.					
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 characterized by the presence of excess hair growth in women in anatomic sites where growth is considered to be a secondary male characteristic and under androgen control (beard, moustache, chest, abdomen)					
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	-	-
Definition: A disorder characterized by excessive perspiration.					

Skin and subcutaneous tissue disorders					
	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 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 destructive means of hair removal to camouflage; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by hair density or length beyond the accepted limits of normal in a particular body region, for a particular age or race.					
Hypohidrosis	-	Symptomatic; limiting instrumental ADL	Increase in body temperature; limiting self care ADL	Heat stroke	Death
Definition: A disorder characterized by reduced sweating.					
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 characterized by hypertrophy of the subcutaneous adipose tissue at the site of multiple subcutaneous injections of insulin.					
Nail discoloration	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characterized by a change in the color of the nail plate.					
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 characterized by loss of all or a portion of the nail.					
Nail ridging	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characterized 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 characterized by marked discomfort sensation in the skin.					
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	-	-
Definition: A disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of the hands or the soles of the feet.					
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 characterized by swelling due to an excessive 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
Definition: A disorder characterized by an increase in sensitivity of the skin to light.					

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 characterized 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	-	-
Definition: A disorder characterized by hemorrhagic areas of the skin and mucous membrane. Newer lesions appear reddish in color. Older lesions are usually a darker purple color and eventually become a brownish-yellow 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; life-threatening consequences	Death
Definition: A disorder characterized by an eruption of papules and pustules, typically appearing in face, 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	-	-
Definition: A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbillform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and associated with pruritus.					
Scalp pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation 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 characterized by the degeneration and thinning of the epidermis and dermis.					
Skin hyperpigmentation	Hyperpigmentation covering <10% BSA; no psychosocial impact	Hyperpigmentation covering >10% BSA; associated psychosocial impact	-	-	-
Definition: A disorder characterized 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 characterized 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 characterized by an area of hardness in the skin.					
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
Definition: A disorder characterized by circumscribed, inflammatory and necrotic erosive lesion on the skin.					

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 characterized by less than 10% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.					
Telangiectasia	Telangiectasias covering <10% BSA	Telangiectasias covering >10% BSA; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by local dilatation of small vessels resulting in red discoloration of 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 characterized by greater than 30% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the 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 at age 40 - 45 years of age	Menopause occurring before age 40 years of age	-	-
Definition: A disorder characterized by the permanent cessation of menses, usually defined by 12 consecutive months of amenorrhea in 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 procedures - 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

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
Definition: A disorder characterized by leakage of intravascular fluids into the extravascular space. This syndrome is observed in patients who demonstrate a state of generalized leaky capillaries following shock syndromes, low-flow states, ischemia-reperfusion injuries, toxemias, medications, or poisoning. It can lead to generalized edema and multiple organ 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 characterized by episodic reddening of the face.					
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 characterized by a localized collection of blood, usually clotted, in an organ, space, or tissue, due to a break in the 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 characterized by an uncomfortable and temporary sensation of intense body warmth, flushing, sometimes accompanied 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 WNL; monotherapy indicated Pediatric: recurrent or persistent (>=24 hrs) BP >ULN; monotherapy indicated	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 characterized by a pathological increase in blood pressure; a repeatedly elevation in the blood pressure exceeding 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 characterized by a blood pressure that is below the normal expected for an individual 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
Definition: A disorder characterized by the loss of lymph fluid into the surrounding tissue or body cavity.					
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 characterized 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 characterized by a cystic lesion containing lymph.					
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 characterized by impaired circulation to an extremity.					
Phlebitis	-	Present	-	-	-
Definition: A disorder characterized by inflammation of the wall of a vein.					
Superficial thrombophlebitis	-	Present	-	-	-
Definition: A disorder characterized by a blood clot and inflammation involving a superficial vein of the extremities.					

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 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 characterized by occlusion of a vessel by a thrombus 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 characterized by inflammation involving the wall 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 characterized 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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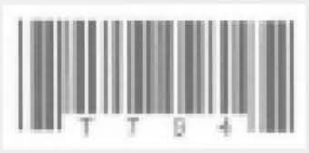

Appendix B: Pemphigus Disease Area Index

- Skin - Activity - Damage

Anatomical Location	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 > 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				
Legs				
Feet				
Genitals				
Total skin	**/120**			**/12**

- Scalp

Scalp	Erosion/Blisters or new erythema	Number lesions if 3		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 membrane

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**	

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

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

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

For SAE reporting:	For any other questions or to contact the Medical Monitor:
Medpace Clinical Safety Medpace SAE hotline: Telephone: PPD dial P or PPD PPD dial P D Facsimile: PPD or PPD e-mail: PPD	PPD PPD Mobile phone: PPD Office phone: PPD ext. PPD

SAE CRITERIA

* A serious adverse event (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.

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: 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) **Exploratory objectives** • 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) o 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 ≥ 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 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 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; 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; 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, and administration	SYNT001 **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 70 days (10 weeks): Screening of up to 2 weeks (14 days); dosing period of 4 weeks (28 days); and 4 weeks (28 days) of follow-up

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 (*FCGR2A* 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}, $AUC_{0-24,}$ and $AUC_{0-\infty.}$
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	
C3 and AECA[l]		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.*																

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

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
l: 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

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:
  - 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)

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:
  - Serum anti-epithelial cell antibody (AECA) levels by indirect immunofluorescence
  - Circulating immune complexes (CIC)
  - 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

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 (AUC_{0-24}), and area under the plasma concentration-time curve from pre-dose (time 0) to infinity ($AUC_{0-\infty}$)

PD Biomarkers:

- Ig Assessments: Serial assessments of total IgG and IgG subtypes (IgG1-4)
  - Serial assessments of total IgG and IgG subtypes (IgG1-4)
  - IgA levels
  - 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 ≥ 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 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;
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 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 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.

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

7.10 Treatment Day 21 (Dose 4)

On Day 21, (± 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
- 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 (± 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 ± 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 ± 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 ± 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 (± 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 (± 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 ≥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 ± 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 (2ºC to 8ºC/36ºF to 46ºF) 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

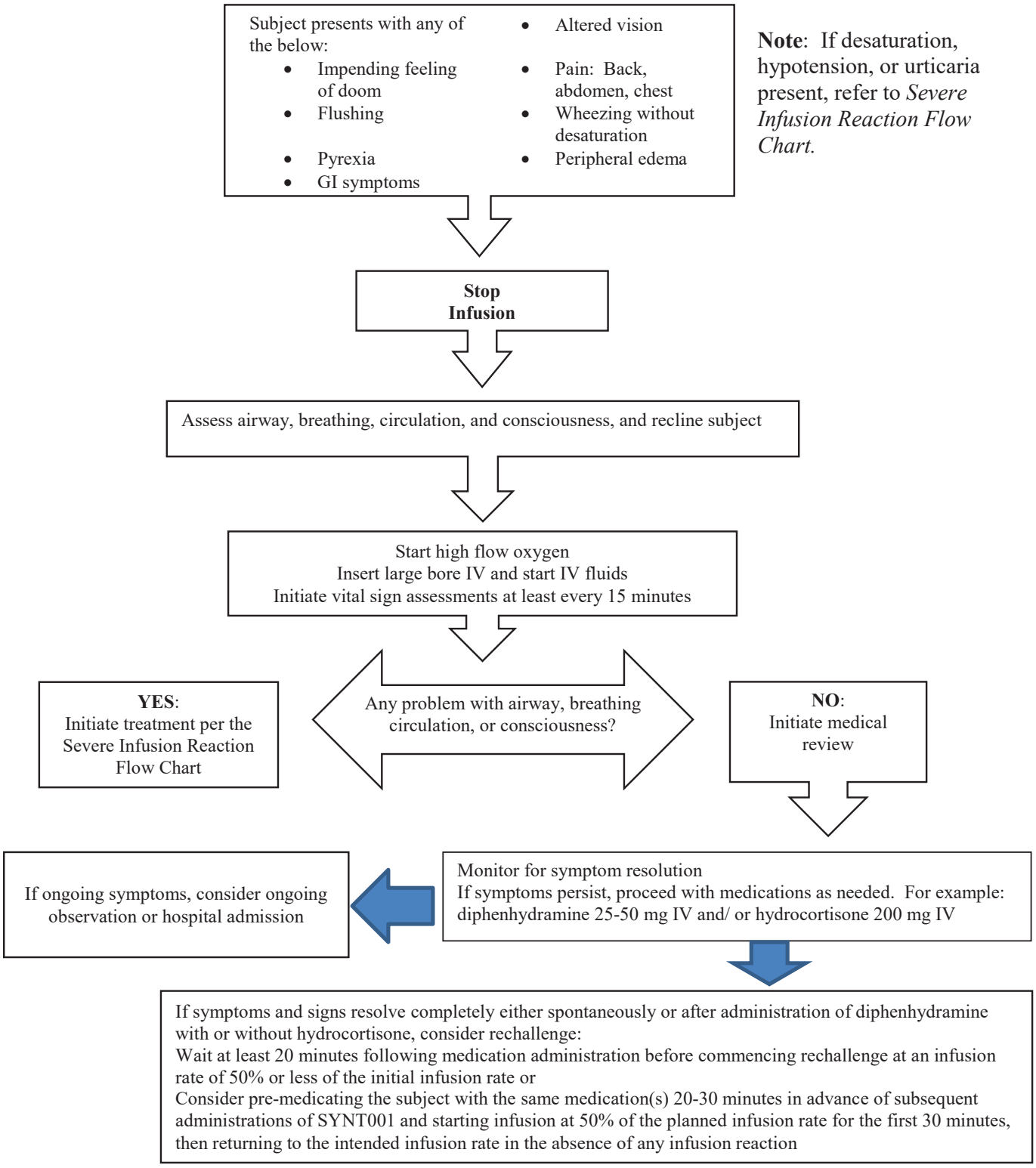

Figure 2: Management of Severe (Grade 3 or higher) Infusion Reactions

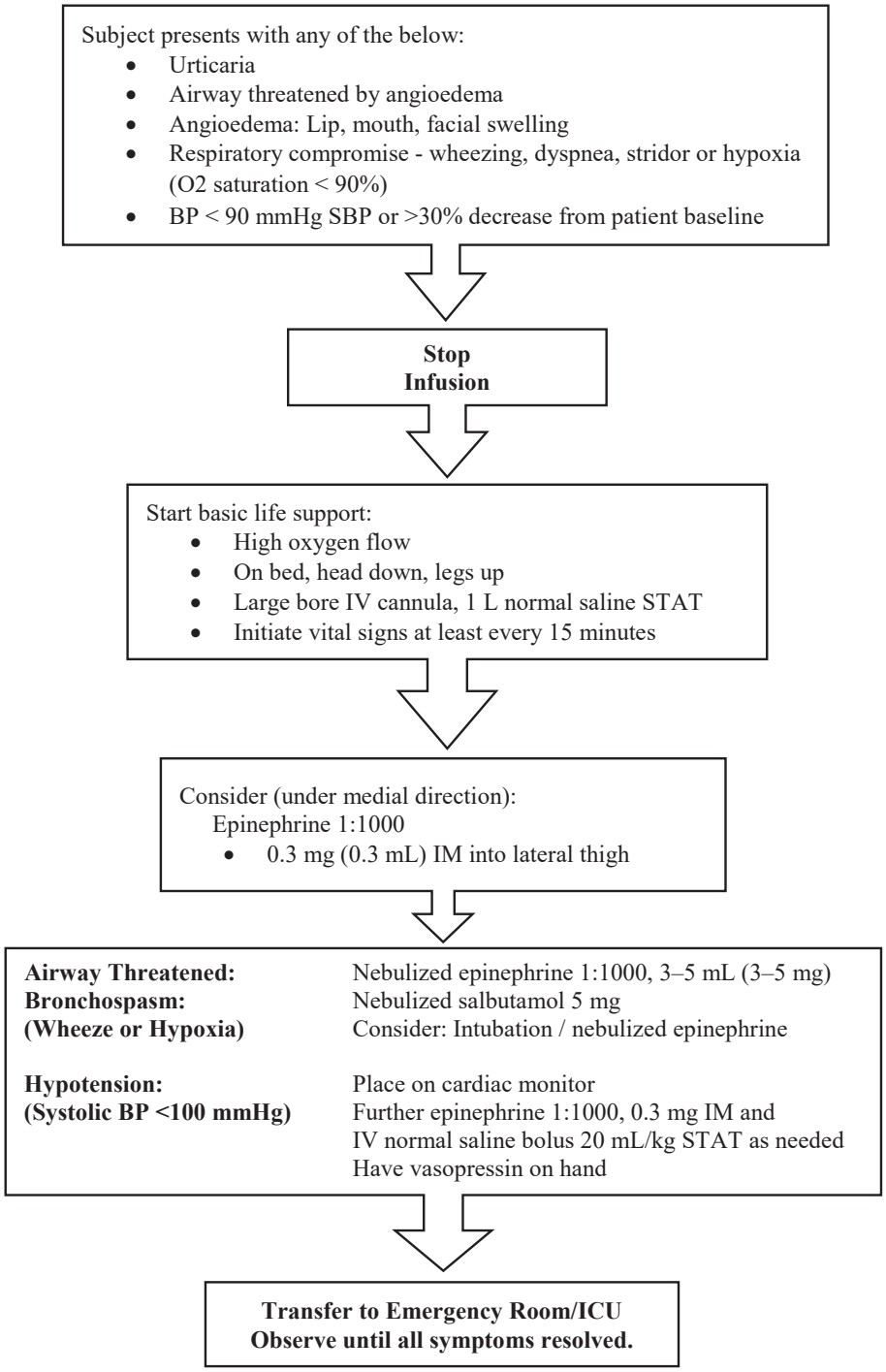

Table 5: Grading and Management of Allergic or Infusion-Related Reactions

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:

- **Death:** 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.

- **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:**
  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**
- **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.

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 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:

Medpace Clinical Safety
Medpace SAE hotline:
Telephone: PPD dial PP or PPD dial PP
Facsimile: PPD or PPD
e-mail: PPD

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

Medical Safety Contact
PPD
Phone (US): PPD extension PPD
Mobile phone: PPD
Email: PPD

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

Sponsor Contact:	PPD PPD Phone: PPD Email: PPD
Sponsor Medical Director:	PPD PPD Phone: PPD Email: PPD
Medical Monitor:	PPD Medpace 43 Thorndike Street Cambridge, MA 01240 Phone: PPD Email: PPD
Study Monitoring:	Medpace 5375 Medpace Way Cincinnati, OH 45227 Phone (Main): PPD Email: PPD

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	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 > 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	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 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 membrane

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**	

Total Activity Score: ☐ **Total Damage Score** ☐

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
Original Protocol:	28 January 2017
Amendment 1.1	21 March 2017

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 2017
Amendment 1.1:	21 March 2017
Amendment 2.0	12 April 2017

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 Medpace SAE hotline: Telephone: PPD dial P P or PPD PPD dial P D Facsimile: PPD or PPD PPD	PPD PPD Mobile phone: PPD Office phone: PPD ext. PPD

SAE CRITERIA

* A serious adverse event (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.

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: 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) **Exploratory objectives** • 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) o 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 ≤ 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 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; 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; 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, and administration	SYNT001 **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. 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 (*FCGR2A* 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}, $AUC_{0-24,}$ and $AUC_{0-\infty.}$
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

	Screening	Treatment Period															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[l]		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 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*																	

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

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
l: 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	± 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

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:
  - 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)

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:
  - Serum anti-epithelial cell antibody (AECA) levels by indirect immunofluorescence
  - Circulating immune complexes (CIC)
  - 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

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 (AUC_{0-24}), and area under the plasma concentration-time curve from pre-dose (time 0) to infinity ($AUC_{0-\infty}$)

PD Biomarkers:

- Ig Assessments: Serial assessments of total IgG and IgG subtypes (IgG1-4)
  - Serial assessments of total IgG and IgG subtypes (IgG1-4)
  - IgA levels
  - 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 ≥ 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 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.

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 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 $\leq$ 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 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)	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 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 ± 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 ± 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 ± 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 (± 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 (± 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 (± 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
  - CIC
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.10 Treatment Day 21 (Dose 4)

On Day 21, (± 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
- 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 (± 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 ± 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 ± 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 ± 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 (± 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
- Concomitant medication assessment (Section 6.9)
- AE assessment (Section 6.10)

7.16 Follow-up Day 56

On Day 56 (± 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

- 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 (± 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)

7.18 Follow-up Day 112 (End-of-Study) or Early Termination Visit

On Day 112 (± 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 ≥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 (2ºC to 8ºC/36ºF to 46ºF) 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

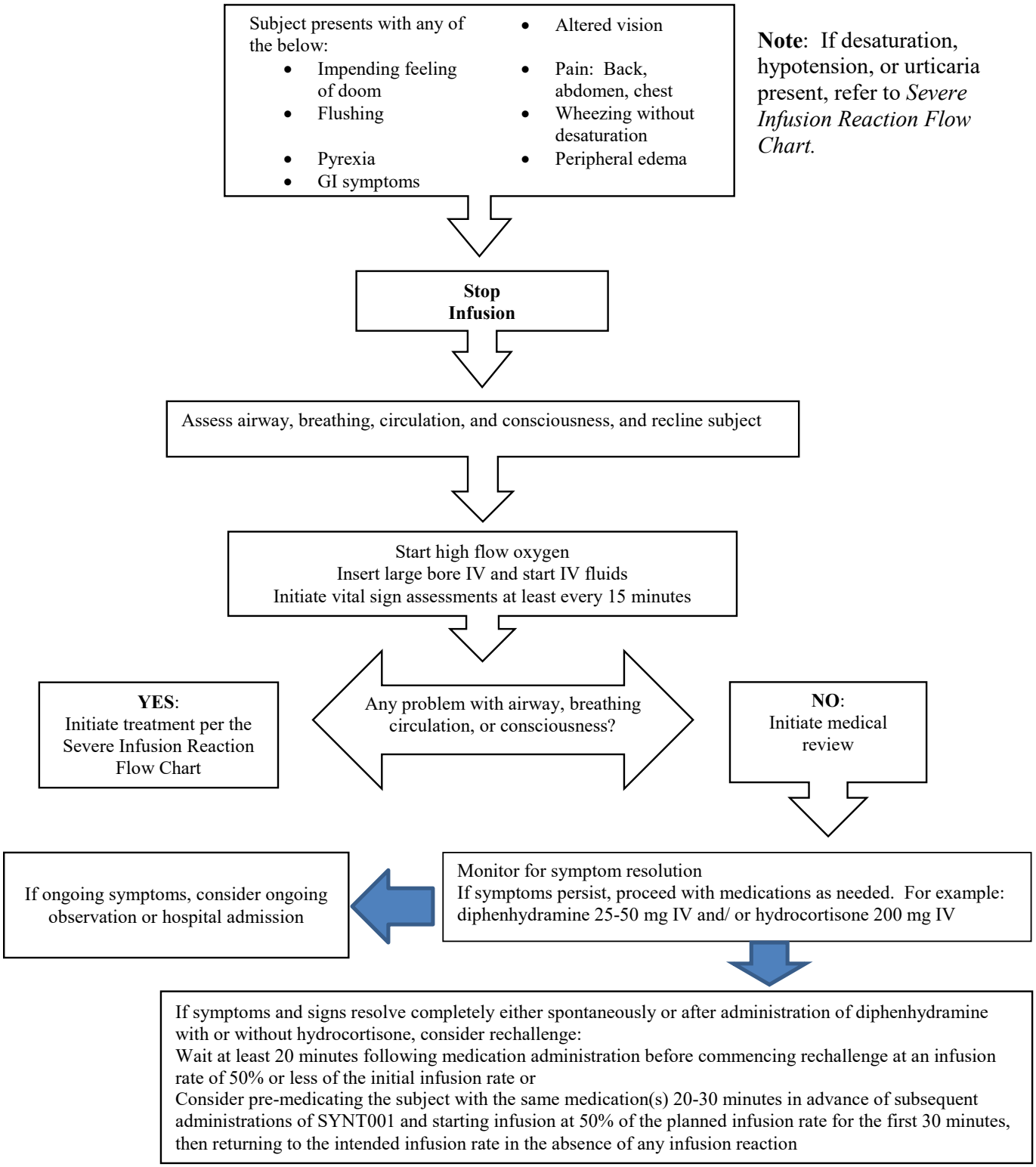

Figure 2: Management of Severe (Grade 3 or higher) Infusion Reactions

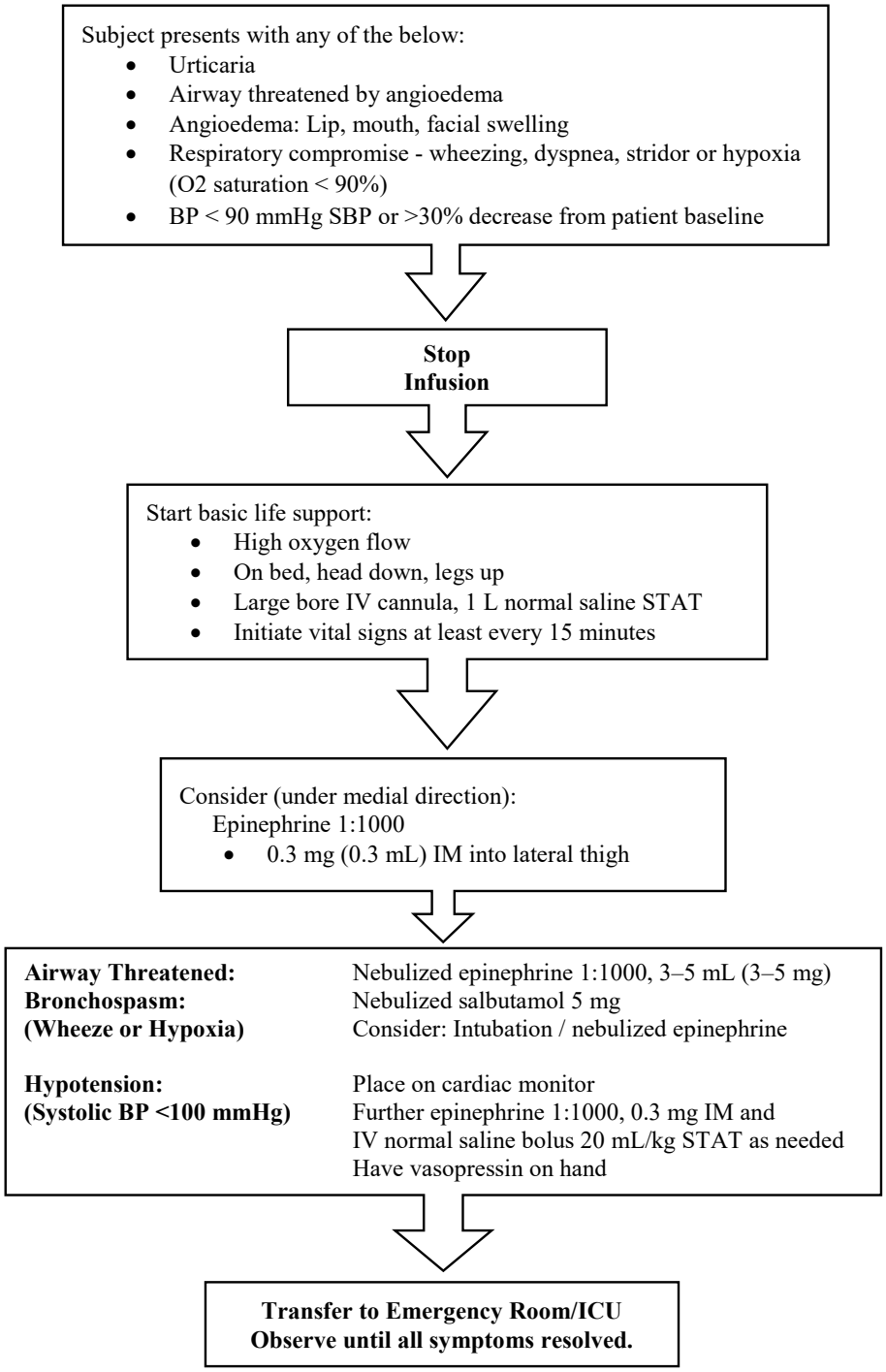

Table 5: Grading and Management of Allergic or Infusion-Related Reactions

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:

- **Death:** 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.

- **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:**
  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**
- **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.

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 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 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:

Medpace Clinical Safety
Medpace SAE hotline:
Telephone: PPD dial PP or PPD dial PP
Facsimile: PPD or PPD
e-mail: PPD

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

Medical Safety Contact
PPD
Phone (US): PPD extension PPD
Mobile phone: PPD
Email: PPD

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

Sponsor Contact:	PPD PPD Phone: PPD Email: PPD
Sponsor Medical Director:	PPD PPD Phone: PPD Email: PPD
Medical Monitor:	PPD Medpace 43 Thorndike Street Cambridge, MA 01240 Phone: PPD Email: PPD
Study Monitoring:	Medpace 5375 Medpace Way Cincinnati, OH 45227 Phone (Main): PPD Email: PPD

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

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 > 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	**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 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 membrane

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**	

Total Activity Score: ☐ **Total Damage Score** ☐

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: **Amendment 1.1** **Amendment 2.0**	Original, 18 January 2017 21 March 2017 12 April 2017

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 (~~1~~0 *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**:
    - 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 *112*~~56~~. 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.)

- **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 84*~~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 *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 *56*~~42~~ for safety assessments, study drug dosing, sample collections, and other study procedures.
- Subjects also will return to the clinic on Day*s 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 visits*~~28 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

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 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 1–2 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 *112*~~56~~. The total blood draw for each subject who completes the study at Day *112*~~56~~, will be approximately ~~311~~ *381* mL. Please refer to the Laboratory Manual for more information.
- **Table 3: Clinical Laboratory Panels, Hematology**
    - 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 Day*s* 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 84*~~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 *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 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 *112*~~56~~.
• Circulating immune complexes (CIC)	Days 0, 5, 7, 12, 14, 19, 21, 28, 33, 42, *56, 84* and *112*~~56~~
• Albumin	Screening, and Days 0, 7, 14,21, 28, 33, 42, *56, 84* and *112*~~56~~
• Anti-Dsg (1 and 3) antibody titer	Screening, Days 0, 7, 14, 33, *56, 84* and *112*~~56~~
• 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 ~~28~~*56*
• Exploratory biomarker (*FCGR2A* SNP)	Day 0

Section 6.7.6 Immunogenicity Testing

- ~~Up to 4 s~~*S*erum samples will be collected for immunogenicity analyses~~. Samples will be collected~~ on Days 0 (pre-dose), 14, 28, *56, 84* and ~~56~~*112*

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 *112*~~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.

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 *84*~~56~~ to analyze SYNT001 levels

SECTION 7 STUDY ASSESSMENTS

Section 7.7 Dose 2 Follow-up Day 12

- On Day 12 (± 6 hours) the subject *may* ~~will~~ return to the clinic, or be visited by an at-home 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 *6.6*~~6.5~~)
- 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 (± 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)*

Section 7.18 Follow-up Day 112 (End-of-Study) or Early Termination Visit

On Day 112 (± 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 visits*~~28 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 ~~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 *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 ~~700~~*500*-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*~~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 *used for the inclusion criteria* of ~~700~~*600* mg/dL *in this study* would be to ~~350~~300 mg/dL. An 80% decrease from baseline after multiple doses would result in IgG levels of 230 mg/dL and ~~140~~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, 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 ~~may~~*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*.

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

- **Death:** This includes any death that occurs while the subject is "on study" t*hrough 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.

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,

PPD

PPD

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)

Current Text: 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.

Revised text: 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*

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.

Rationale: 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

Rationale: 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:

Current 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

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.*

Rationale**:** 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)

Current text: 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 medication*s* and treatment*s* 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, pre-medications 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-

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)

Current text: "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)."

Rationale: 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, Inc.

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/m^2

Revised text: Body mass index (BMI) 18.5 – 39.9 kg/m^2

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.

PPD

[redacted]

Syntimmune, Inc.

257 Park Ave S, 15th Floor, New York, New York, 10010

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 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

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	10-10-2017
	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 Medpace SAE hotline: Telephone: PPD dial PPD or PPD PPD dial PPD Facsimile: PPD or PPD e-mail: PPD	PPD PPD Mobile phone: PPD PPD Office phone: PPD ext. PPD

SAE CRITERIA

* A serious adverse event (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.

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: 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) **Exploratory objectives** • 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) o 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) ○ 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).
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 ≤ 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 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;

	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, 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
Study drug, dosage, and administration	SYNT001 **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	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 (*FCGR2A* 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.

- 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}, $AUC_{0-24,}$ and $AUC_{0-\infty.}$
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

• 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															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[l]		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 collected from within 14 days prior to Day 0 through the last study visit*																	

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

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
l: 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	± 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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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

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:
  - 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)

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:
  - Serum anti-epithelial cell antibody (AECA) levels by indirect immunofluorescence
  - Circulating immune complexes (CIC)
  - 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)
  - 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 (AUC_{0-24}), and area under the plasma concentration-time curve from pre-dose (time 0) to infinity ($AUC_{0-\infty}$)

PD Biomarkers:

- Ig Assessments: Serial assessments of total IgG and IgG subtypes (IgG1-4)
  - Serial assessments of total IgG and IgG subtypes (IgG1-4)
  - IgA levels
  - 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 ≥ 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 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 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.

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 $\leq$ 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 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 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, 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 ± 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 ± 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 ± 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 (± 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 (± 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 (± 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 (± 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, (± 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 (± 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 ± 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 ± 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 ± 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 (± 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 (± 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 (± 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 (± 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 ≥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 (2ºC to 8ºC/36ºF to 46ºF) 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

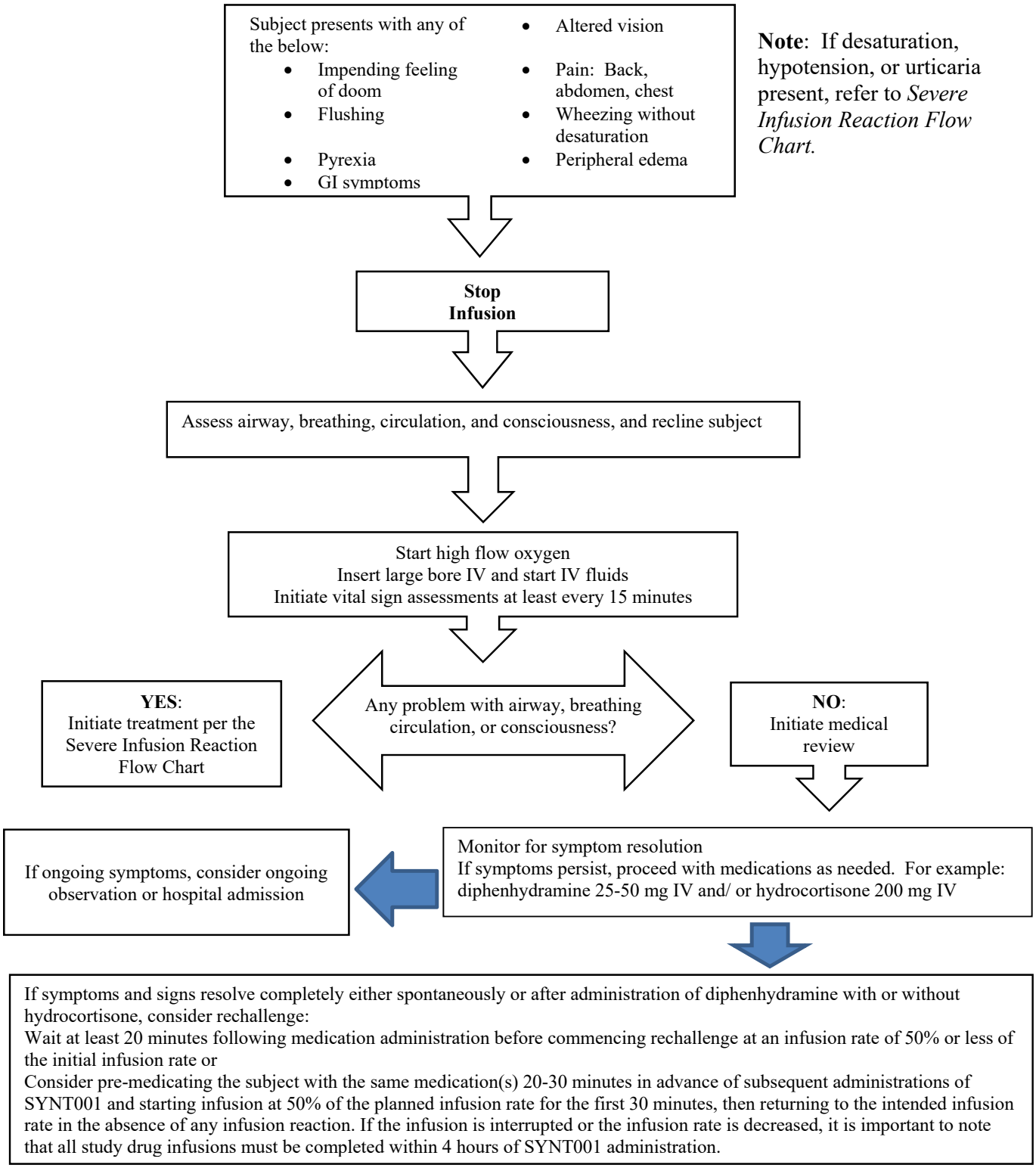

Figure 2: Management of Severe (Grade 3 or higher) Infusion Reactions

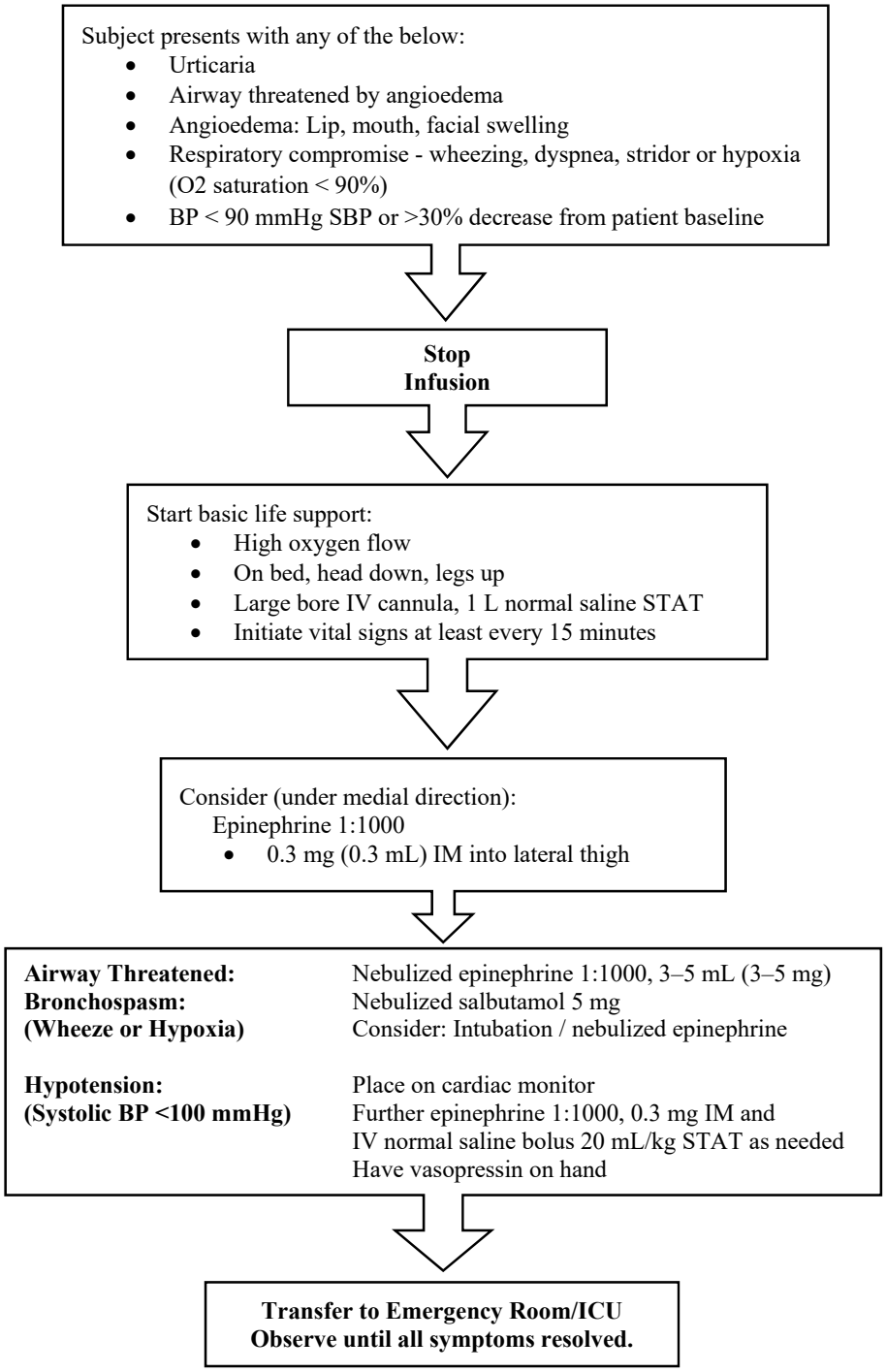

Table 5: Grading and Management of Allergic or Infusion-Related Reactions

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:

- **Death:** 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.

- **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:**
  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**
- **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.

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 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 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:

Medpace Clinical Safety
Medpace SAE hotline:
Telephone: PPD dial PP or PPD dial PP
Facsimile: PPD or PPD
e-mail: PPD

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

Medical Safety Contact
PPD
Phone (EU): PPD extension PPD
Mobile phone: PPD
Email: PPD

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

Sponsor Contact and Medical Director:	PPD PPD Phone: PPD Email: PPD
Medical Monitor:	PPD Medpace Wallace House 17-21 Maxwell Place Stirling, Scotland FK81JU Phone: PPD extension PPD Email: PPD
Study Monitoring:	Medpace 5375 Medpace Way Cincinnati, OH 45227 Phone (Main): PPD Email: PPD

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

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 *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 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.

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† 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).

CONTENTS

Blood and lymphatic system disorders					
	Grade				
Adverse Event	1	2	3	4	5
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	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
Definition: A disorder characterized by an reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.					
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 characterized by the inability of the bone marrow to produce hematopoietic elements.					
Disseminated intravascular coagulation	-	Laboratory findings with no bleeding	Laboratory findings and bleeding	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by systemic pathological activation of blood clotting mechanisms which results in clot formation throughout the body. There is an increase in the risk of hemorrhage as the body is depleted of platelets and coagulation factors.					
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 characterized by an ANC <1000/mm3 and 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.					
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 characterized by laboratory test results that indicate widespread erythrocyte cell 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 characterized by a form of thrombotic microangiopathy with renal failure, hemolytic anemia, and severe thrombocytopenia.					
Leukocytosis	-	-	>100,000/mm3	Clinical manifestations of leucostasis; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate an increased number of white blood cells in the blood.					
Lymph node 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 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 spleen.					
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
Definition: A disorder characterized by the presence of microangiopathic hemolytic anemia, thrombocytopenic purpura, fever, renal abnormalities and neurological abnormalities such as seizures, hemiplegia, and visual disturbances. It is an acute or subacute condition.					
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
Definition: A disorder characterized by signs and symptoms related to acute ischemia of the myocardium secondary to coronary artery disease. The clinical presentation covers a spectrum of heart diseases from unstable angina to myocardial infarction.					
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 characterized by a defect in aortic valve function or structure.					
Asystole	Periods of asystole; non-urgent medical management indicated	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia without cardiac electrical activity. Typically, this is accompanied by cessation of the 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 characterized by a dysrhythmia without discernible P waves and an irregular ventricular response due to multiple reentry circuits. The rhythm disturbance originates above the ventricles.					
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 characterized by a dysrhythmia with organized rhythmic atrial contractions with a rate of 200-300 beats per minute. The rhythm disturbance originates in the atria.					
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 characterized by a dysrhythmia with complete 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	-	-	-
Definition: A disorder characterized by a dysrhythmia with a delay in the time required for the conduction of an electrical impulse through the atrioventricular (AV) node beyond 0.2 seconds; prolongation of the PR interval greater than 200 milliseconds.					
Cardiac arrest	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by cessation of the pumping function of the heart.					
Chest pain - cardiac	Mild pain	Moderate pain; limiting instrumental ADL	Pain at rest; limiting self care ADL	-	-
Definition: A disorder characterized by substernal discomfort due to insufficient myocardial oxygenation.					
Conduction disorder	Mild symptoms; intervention not indicated	Moderate symptoms	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized 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 characterized by a thickened and fibrotic pericardial sac; these fibrotic changes impede normal myocardial function by restricting myocardial muscle 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 support)	Death
Definition: A disorder characterized by the inability of the heart to pump blood at an adequate volume to meet tissue metabolic requirements, or, the ability to do so only at an elevation in the filling pressure.					

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
Definition: A disorder characterized by failure of the left ventricle to produce adequate output despite an increase in distending pressure and in end-diastolic volume. Clinical manifestations mayinclude dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.					
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 characterized by a defect in mitral valve function 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
Definition: A disorder characterized by a dysrhythmia with relatively constant PR interval prior to the block of an atrial impulse. This is the result of intermittent failure of atrial electrical impulse conduction through the atrioventricular (AV) node to the ventricles.					
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
Definition: A disorder characterized by a dysrhythmia with a progressively lengthening PR interval prior to the blocking of an atrial impulse. This is the result of intermittent failure of atrial electrical impulse conduction through the atrioventricular (AV) node to the ventricles.					
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 characterized by gross necrosis of the myocardium; this is due to an interruption 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 characterized by inflammation of the muscle tissue of the heart.					
Palpitations	Mild symptoms; intervention not indicated	Intervention indicated	-	-	-
Definition: A disorder characterized by an unpleasant sensation of irregular and/or forceful beating of 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 characterized by a dysrhythmia with abrupt onset and sudden termination of atrial contractions with a rate of 150-250 beats per minute. The rhythm disturbance originates in the atria.					
Pericardial effusion	-	Asymptomatic effusion size small to moderate	Effusion with physiologic consequences	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by fluid collection within the pericardial sac, usually due to inflammation.					
Pericardial tamponade	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in intrapericardial pressure due to the collection of blood or fluid in the pericardium.					
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
Definition: A disorder characterized by irritation to the layers of the pericardium (the protective sac around the heart).					

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 characterized by a defect in pulmonary valve function or structure.					
Restrictive cardiomyopathy	-	-	Symptomatic heart failure or other cardiac symptoms, responsive to intervention	Refractory heart failure or other poorly controlled cardiac symptoms	Death
Definition: A disorder characterized by an inability of the ventricles to fill with blood because the myocardium (heart muscle) stiffens and loses its flexibility.					
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 characterized by impairment of right ventricular function associated with low ejection fraction and a decrease in motility 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
Definition: A disorder characterized by a dysrhythmia with alternating periods of bradycardia and atrial tachycardia accompanied by syncope, fatigue and dizziness.					
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 characterized by a dysrhythmia with a heart rate 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 characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates in the sinus node.					
Supraventricular tachycardia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates above the ventricles.					
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 characterized by a defect in tricuspid valve function 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 characterized by a dysrhythmia that originates in the ventricles.					
Ventricular fibrillation	-	-	-	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia without discernible QRS complexes due to rapid repetitive excitation of myocardial fibers without coordinated contraction of the ventricles.					
Ventricular tachycardia	-	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates distal to the bundle 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 characterized by the presence of an accessory conductive pathway between the atria and the ventricles that causes premature ventricular activation.					
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 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 characterized by a sensation of marked discomfort 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 characterized by inflammation, swelling and redness to the outer ear and ear canal.					
External ear 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 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 aids; threshold shift >20 dB at 3 kHz and above in at least one ear; additional speech-language related services indicated.	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.	-
Definition: A disorder characterized by partial or complete loss of the ability to detect or understand sounds resulting from damage to ear structures.					
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
Definition: A disorder characterized by inflammation (physiologic response to irritation), swelling and redness to the middle ear.					
Tinnitus	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by noise in the ears, such as ringing, buzzing, roaring or clicking.					
Vertigo	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation as if the external world were revolving around the patient (objective vertigo) or as if he himself were revolving in space (subjective vertigo).					
Vestibular disorder	-	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dizziness, imbalance, nausea, 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	Moderate symptoms; medical intervention indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder that occurs when the adrenal cortex does not produce enough of the hormone cortisol and in some cases, the hormone aldosterone. It may be due to a disorder of the adrenal cortex as in Addison's disease or primary adrenal insufficiency.					
Cushingoid	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms, medical intervention or hospitalization indicated	-	-
Definition: A disorder characterized by signs and symptoms that resemble Cushing's disease or syndrome: buffalo hump obesity, striations, adiposity, hypertension, diabetes, and osteoporosis, usually due to exogenous corticosteroids.					
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 characterized by unusually late sexual maturity.					
Growth accelerated	-	>= +2 SD (standard deviation) above mid parental height or target height	-	-	-
Definition: A disorder characterized by greater growth than expected for age.					
Hyperparathyroidism	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by an increase in production of parathyroid hormone by the parathyroid glands. This results in hypercalcemia (abnormally high levels of calcium in the blood).					
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 characterized by excessive levels of thyroid hormone in the body. Common causes include an overactive thyroid gland or thyroid hormone overdose.					
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 characterized by a decrease in production of parathyroid hormone by the parathyroid 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 characterized by a decrease in production of thyroid hormone by the thyroid gland.					
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 characterized by unusually early development of secondary sexual features; the onset of sexual maturation begins usually before age 8 for girls and before age 9 for boys.					
Virilization	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by inappropriate masculinization occurring in a female or prepubertal 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 disorders					
	Grade				
Adverse Event	1	2	3	4	5
Blurred vision	Intervention not indicated	Symptomatic; limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by visual perception of unclear or fuzzy images.					
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., cataract surgery)	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by partial or complete opacity of the crystalline lens of one or both eyes. This results in a decrease in visual acuity and eventual blindness if untreated.					
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 characterized by inflammation, swelling and redness to the conjunctiva of the eye.					
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 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	Symptomatic; multiple agents indicated; limiting instrumental ADL	Decrease in visual acuity (<20/40); limiting self care ADL	-	-
Definition: A disorder characterized 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 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 characterized by a sensation of marked discomfort in the eye.					
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 characterized by impaired eyelid function.					
Flashing lights	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by a sudden or brief burst of light.					
Floaters	Symptomatic but not limiting ADL	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.					
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 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	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 characterized by inflammation to the cornea of the eye.					
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 characterized by an inability to see clearly in dim light.					

Eye disorders					
	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	-
Definition: A disorder characterized by involvement of the optic nerve (second cranial nerve).					
Papilledema	Asymptomatic; no visual field defects	Symptomatic decline in 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 characterized by swelling around the optic disc.					
Photophobia	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by fear and avoidance of 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 characterized by the separation of the inner retina layers from the underlying 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 characterized by a small laceration of the retina, this occurs when the vitreous separates from the retina. Symptoms include flashes and floaters.					
Retinal vascular disorder	-	Topical medication indicated	Intravitreal medication; operative intervention indicated	-	-
Definition: A disorder characterized by pathological retinal blood vessels that adversely affects 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 involving 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 characterized by involvement of the sclera of the eye.					
Uveitis	Asymptomatic; clinical or diagnostic observations only	Anterior uveitis; medical intervention indicated	Posterior or pan-uveitis	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by inflammation to the uvea of the eye.					
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 characterized by blood extravasation into the vitreous humor.					
Watering eyes	Intervention not indicated	Intervention indicated	Operative intervention indicated	-	-
Definition: A disorder of excessive tearing in the eyes; it can be caused by overproduction 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 disorders					
	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 characterized by swelling of the abdomen.					
Abdominal 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 abdominal region.					
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 characterized 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 characterized by bleeding from the anal region.					
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 characterized 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
Definition: A disorder characterized by a necrotic process occurring in the anal region.					
Anal 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 anal region.					
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 characterized 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 characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the anal canal.					
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 characterized by accumulation of serous or hemorrhagic 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 characterized by subject-reported feeling of uncomfortable fullness of the abdomen.					
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 characterized 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	-	-
Definition: A disorder characterized by inflammation of the lip.					

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
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 characterized 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 characterized 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 characterized by bleeding from the colon.					
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
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents in the colon.					
Colonic perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the colonic wall.					
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 characterized 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 characterized by a circumscribed, inflammatory 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 characterized by irregular and infrequent or difficult 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 characterized by the decay of a tooth, in which 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 characterized by frequent and watery bowel movements.					
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	-	-
Definition: A disorder characterized by reduced salivary flow in the oral cavity.					

Gastrointestinal disorders					
	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 characterized by an abnormal communication between the duodenum and another 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 characterized by bleeding from the duodenum.					
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 characterized 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 characterized by a rupture in the duodenal wall.					
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 characterized 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 characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the duodenal wall.					
Dyspepsia	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; surgical intervention indicated	-	-
Definition: A disorder characterized by an uncomfortable, often painful feeling in the stomach, resulting from impaired digestion. Symptoms include burning stomach, bloating, heartburn, nausea and vomiting.					
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 characterized by difficulty in swallowing.					
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 characterized by inflammation of the small and 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 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	Life-threatening consequences; urgent intervention indicated	Death
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 or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the esophagus.					

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 characterized by a necrotic process occurring 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 characterized by blockage of the normal flow of the contents in the esophagus.					
Esophageal 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 esophageal region.					
Esophageal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the wall of the esophagus.					
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 characterized 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 characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the esophageal 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 characterized by bleeding from esophageal varices.					
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 characterized by inflammation of the esophageal wall.					
Fecal incontinence	Occasional use of pads required	Daily use of pads required	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by inability to control the escape of stool from the rectum.					
Flatulence	Mild symptoms; intervention not indicated	Moderate; persistent; psychosocial sequelae	-	-	-
Definition: A disorder characterized by a state of excessive gas in the alimentary canal.					
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 characterized by an abnormal communication between the stomach and another organ or anatomic site.					
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 characterized by bleeding from the gastric wall.					
Gastric 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 characterized by a necrotic process occurring in the gastric wall.					

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Gastric perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the stomach wall.					
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 characterized 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
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the stomach.					
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 characterized by inflammation of the stomach.					
Gastroesophageal reflux disease	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; surgical intervention indicated	-	-
Definition: A disorder characterized by reflux of the gastric and/or duodenal contents into the distal esophagus. It is chronic in nature and usually caused by incompetence of the lower esophageal sphincter, and may result in injury to the esophageal mucosal. Symptoms include heartburn and acid indigestion.					
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 characterized by an abnormal communication between any part of the gastrointestinal 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 characterized by a sensation of marked discomfort in the gastrointestinal region.					
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 characterized by an incomplete paralysis of the muscles of the stomach wall resulting in delayed emptying of the gastric contents into the small intestine.					
Gingival pain	Mild pain	Moderate pain interfering with oral intake	Severe pain; inability to aliment orally	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the gingival region.					
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 characterized by bleeding from the hemorrhoids.					
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 characterized by the presence of dilated veins in the rectum and surrounding area.					
Ileal 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 characterized by an abnormal communication between the ileum and another organ or anatomic site.					
Ileal 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 characterized by bleeding from the ileal wall.					

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Ileal 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 characterized by blockage of the normal flow of the intestinal contents in the ileum.					
Ileal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the ileal wall.					
Ileal 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 characterized by a narrowing of the lumen of the ileum.					
Ileal 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 characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the ileum.					
Ileus	-	Symptomatic; altered GI function; bowel rest indicated	Severely altered GI function; TPN indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by failure of the ileum to transport intestinal contents.					
Intra-abdominal hemorrhage	-	Medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding in the abdominal cavity.					
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 characterized by an abnormal communication between the jejunum and another 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 characterized by bleeding from the jejunal wall.					
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 characterized by blockage of the normal flow of the intestinal contents in the jejunum.					
Jejunal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized 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 characterized 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 characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the jejunum.					
Lip pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort of the lip.					

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Lower 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 characterized by bleeding from the lower gastrointestinal 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 characterized by inadequate absorption of nutrients in the small intestine. Symptoms include abdominal marked 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 characterized by inflammation of the oral mucosal.					
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 characterized by a queasy sensation and/or the urge to vomit.					
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 characterized by blockage of the normal flow of the contents in the stomach.					
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 characterized by an abnormal communication between the oral cavity and another 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 characterized by a burning or tingling sensation on the lips, tongue or entire mouth.					
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 characterized by bleeding from the mouth.					
Oral 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 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 characterized 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 characterized by an abnormal communication between the pancreas and another organ or anatomic site.					
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 characterized by bleeding from the pancreas.					
Pancreatic necrosis	-	-	Tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized 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
Definition: A disorder characterized by inflammation of the pancreas.					
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 gingival 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 characterized 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 characterized 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 characterized by an abnormal communication 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 characterized 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 characterized 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 characterized 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 characterized by blockage of the normal flow of the intestinal contents in the rectum.					
Rectal 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 rectal region.					
Rectal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized 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 characterized 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
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the rectum.					

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
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 characterized by bleeding from the retroperitoneal area.					
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 characterized 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 characterized by an abnormal communication between a salivary gland and another 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 characterized 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 characterized 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 characterized by a rupture in the small intestine 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 characterized 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 characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the small intestine.					
Stomach 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 stomach.					
Tooth development disorder	Asymptomatic; hypoplasia of tooth or enamel	Impairment correctable with oral surgery	Maldevelopment with impairment not surgically correctable; disabling	-	-
Definition: A disorder characterized by a pathological process of the teeth occurring during tooth development.					
Tooth discoloration	Surface stains	-	-	-	-
Definition: A disorder characterized by a change in tooth hue or tint.					
Toothache	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 tooth.					

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 characterized 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 characterized by bleeding from the upper gastrointestinal tract (oral cavity, pharynx, 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 characterized by the reflexive act of ejecting the contents of the stomach through 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

General disorders and administration site conditions					
	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 characterized by a sensation of cold that often marks a physiologic response to sweating after a fever.					
Death neonatal	-	-	-	-	Death
Definition: A disorder characterized by cessation of life occurring during 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 characterized by swelling due to excessive fluid 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 characterized by swelling due to excessive fluid accumulation in the upper or lower 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 characterized by swelling due to excessive fluid accumulation in the trunk area.					
Facial 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 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 characterized by a state of generalized weakness with a pronounced inability to summon sufficient energy to accomplish 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 characterized by elevation of the body's temperature above the upper limit of normal.					
Flu like symptoms	Mild flu-like symptoms present	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by a group of symptoms similar to those observed in patients with the flu. It includes fever, chills, body aches, malaise, loss of appetite and dry cough.					
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 characterized by walking difficulties.					
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
Definition: A disorder characterized by an abnormally low body temperature. Treatment is required when the body temperature is 35C (95F) or below.					

General disorders and administration site conditions					
	Grade				
Adverse 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 (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	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.					
Infusion site extravasation	-	Erythema with associated symptoms (e.g., edema, pain, induration, phlebitis)	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by leakage of a pharmacologic or a biologic substance from the infusion site into the surrounding tissue. Signs and symptoms include induration, erythema, swelling, burning sensation and marked discomfort at the infusion site.					
Injection site reaction	Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)	Pain; lipodystrophy; edema; phlebitis	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an intense adverse reaction (usually immunologic) developing at the site of an injection.					
Irritability	Mild; easily consolable	Moderate; limiting instrumental ADL; increased attention indicated	Severe abnormal or excessive response; limiting self care ADL; inconsolable	-	-
Definition: A disorder characterized by an abnormal responsiveness to stimuli or physiological arousal; may be in response to pain, fright, a drug, an emotional situation or a medical condition.					
Localized edema	Localized to dependent areas, no disability or functional impairment	Moderate localized edema and intervention indicated; limiting instrumental ADL	Severe localized edema and intervention indicated; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to excessive fluid accumulation at a specific anatomic site.					
Malaise	Uneasiness or lack of well being	Uneasiness or lack of well being; limiting instrumental ADL	-	-	-
Definition: A disorder characterized by a feeling of general discomfort or uneasiness, an out-of-sorts feeling.					
Multi-organ failure	-	-	Shock with azotemia and acid-base disturbances; significant coagulation abnormalities	Life-threatening consequences (e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic acidosis)	Death
Definition: A disorder characterized by progressive deterioration of the lungs, liver, kidney and clotting mechanisms.					
Neck edema	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	-	-
Definition: A disorder characterized by swelling due to an accumulation of excessive fluid in the neck.					
Non-cardiac chest pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by discomfort in the chest unrelated to a heart disorder.					
Pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by the sensation of marked discomfort, distress or agony.					
Sudden death NOS	-	-	-	-	Death
Definition: An unexpected cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.					
General disorders and administration site conditions - 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

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 characterized by a narrowing of the lumen of the bile duct.					
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 characterized by an abnormal communication between the bile ducts and another 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 characterized by inflammation involving the gallbladder. It may be associated with 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 characterized by an abnormal communication between the gallbladder and another organ or anatomic site.					
Gallbladder necrosis	-	-	-	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring 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
Definition: A disorder characterized by blockage of the normal flow of the contents of the gallbladder.					
Gallbladder 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 gallbladder region.					
Gallbladder perforation	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the gallbladder wall.					
Hepatic failure	-	-	Asterixis; mild encephalopathy; limiting self care ADL	Moderate to severe encephalopathy; coma; life-threatening consequences	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, lactic dehydrogenase, and alkaline phosphatase.					
Hepatic hemorrhage	Mild; intervention not indicated	Symptomatic; medical intervention indicated	Transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the liver.					
Hepatic necrosis	-	-	-	Life-threatening consequences; urgent radiologic or operative intervention 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 indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the wall of the extrahepatic or intrahepatic bile duct.					

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 characterized by an increase in blood pressure in the portal venous system.					
Portal vein thrombosis	-	Intervention not indicated	Medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized 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; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Immune system disorders					
	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
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.					
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and 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 from loss of function or tissue destruction of an organ or multiple organs, arising from humoral or cellular immune responses of the individual to his own tissue constituents.					
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 characterized by nausea, headache, tachycardia, hypotension, rash, and shortness 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
Definition: A disorder characterized by a delayed-type hypersensitivity reaction to foreign proteins derived from an animal serum. It occurs approximately six to twenty-one days following the administration of the foreign antigen. Symptoms include fever, arthralgias, myalgias, skin eruptions, lymphadenopathy, chest marked discomfort and dyspnea.					
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 infestations					
	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 characterized by an infectious process involving 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
Definition: A disorder characterized by an infectious process involving the anal area and the rectum.					
Appendicitis	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by acute inflammation to the vermiform appendix caused by a pathogenic agent.					
Appendicitis perforated	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by acute inflammation to the vermiform appendix caused by a pathogenic agent with gangrenous changes resulting in the rupture of the appendiceal wall. The appendiceal wall rupture causes the release of inflammatory and bacterial contents from the appendiceal lumen into the abdominal cavity.					
Arteritis infective	-	-	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 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 characterized by an infectious process involving 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 characterized by an infectious process involving 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 characterized by an infectious process involving the bones.					
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
Definition: A disorder characterized by an infectious process involving the breast.					
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 characterized by an infectious process involving 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 characterized 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 infestations					
	Grade				
Adverse Event	1	2	3	4	5
Definition: A disorder characterized by an infectious process involving 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
Definition: A disorder characterized by an infectious process involving the uterine cervix.					
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 characterized by an infectious process involving the conjunctiva. Clinical manifestations 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 characterized by an infectious process involving 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 characterized by an infectious process involving 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
Definition: A disorder characterized by an infectious process involving the use of a medical device.					
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 characterized by an infectious process involving 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 characterized by an infectious process involving the brain tissue.					
Encephalomyelitis infection	-	-	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 brain and spinal cord tissues.					
Endocarditis infective	-	-	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 endocardial layer of the heart.					
Endophthalmitis	-	Local intervention indicated	Systemic intervention or hospitalization indicated	Blindness (20/200 or worse)	-
Definition: A disorder characterized by an infectious process involving the internal structures of the eye.					

Infections and infestations					
	Grade				
Adverse Event	1	2	3	4	5
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: A disorder characterized by an infectious process involving the small and large intestines.					
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 characterized by an infectious process involving 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 characterized by an infectious process involving 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 characterized by an infectious process involving 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 characterized by an infectious process involving 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 characterized by an infectious process involving the liver.					
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 characterized by a viral pathologic process involving 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 characterized by an infectious process involving 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 characterized by an infectious process involving a joint.					
Kidney infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the kidney.					

Infections and infestations					
	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 characterized 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 characterized by an infectious process involving 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 characterized by an infectious process involving 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 characterized by an infectious process involving the lymph nodes.					
Mediastinal infection	-	-	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 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 characterized 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 characterized by an infectious process involving 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 characterized by an infectious process involving 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
Definition: A disorder characterized by an infectious process involving the outer ear and ear canal. Contributory factors include excessive water exposure (swimmer's ear infection) and cuts in the ear canal. Symptoms include fullness, itching, swelling and marked discomfort in the ear and ear drainage.					
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 characterized by an infectious process involving 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 intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the ovary.					

Infections and infestations					
	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 characterized by an infectious process involving 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; life-threatening consequences	Death
Definition: A disorder characterized by an eruption consisting of papules (a small, raised pimple) and pustules (a small pus filled blister), typically appearing in face, scalp, and upper chest and back Unlike acne, this rash does not present with whiteheads or blackheads, and can be symptomatic, with itchy or tender lesions.					
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 characterized by an infectious process involving the soft tissues around the nail.					
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 characterized by an infectious process involving the pelvic cavity.					
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 characterized by an infectious process involving 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
Definition: A disorder characterized by an infectious process involving the orbit of the eye.					
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
Definition: A disorder characterized by an infectious process involving the peripheral nerves.					
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 characterized by an infectious process involving the peritoneum.					
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 characterized 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 characterized by an infectious process involving the vein. Clinical manifestations include erythema, marked discomfort, swelling, and induration along the course of the infected vein.					
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 characterized by an infectious process involving 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 characterized by an infectious process involving 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 characterized by a circumscribed and elevated skin lesion filled with pus.					
Rhinitis 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	-	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 characterized by an infectious process involving 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 characterized by an infectious process involving the scrotum.					
Sepsis	-	-	-	Life-threatening consequences; urgent intervention indicated	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 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 characterized by an infectious process involving 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
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	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the small intestine.					
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 characterized by an infectious process involving soft tissues.					
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				
Adverse Event	1	2	3	4	5
Definition: A disorder characterized by an infectious process involving the spleen.					
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 characterized by an infectious process involving a stoma (surgically created opening 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 characterized by an infectious process involving 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 characterized by an infectious process involving the trachea.					
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 characterized by an infectious process involving the upper respiratory tract (nose, paranasal sinuses, pharynx, larynx, 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 characterized by an infectious process involving 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 characterized by an infectious process involving the urinary tract, most commonly 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 characterized by an infectious process involving the endometrium. It may extend to the myometrium and parametrial 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 characterized by an infectious process involving 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 characterized by an infectious process involving 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 characterized by an infectious process involving the wound.					
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 indicated	Limiting instrumental ADL; operative intervention indicated	Limiting self care ADL; elective surgery indicated	-	-
Definition: A finding of damage to the ankle joint characterized by a break in the continuity of the ankle bone. Symptoms include marked discomfort, swelling and difficulty moving the affected leg and foot.					
Aortic injury	-	-	Severe symptoms; limiting self care ADL; disabling; repair or revision indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to the aorta.					
Arterial injury	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); repair or revision not indicated	Severe symptoms; limiting self care ADL; disabling; repair or revision indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to an artery.					
Biliary 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 bile due to breakdown of a biliary anastomosis (surgical connection of two separate anatomic structures).					
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 of urine due to breakdown of a bladder anastomosis (surgical connection of two separate anatomic structures).					
Bruising	Localized or in a dependent area	Generalized	-	-	-
Definition: A finding of injury of the soft tissues or bone characterized by leakage of blood into surrounding tissues.					
Burn	Minimal symptoms; intervention not indicated	Medical intervention; minimal debridement indicated	Moderate to major debridement or reconstruction indicated	Life-threatening consequences	Death
Definition: A finding of impaired integrity to the anatomic site of an adverse thermal reaction. Burns can be caused by exposure to chemicals, direct heat, electricity, flames and radiation. The extent of damage depends on the length and intensity of exposure and time until provision of treatment.					
Dermatitis radiation	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 cutaneous inflammatory reaction occurring as a result of exposure to biologically effective levels of ionizing radiation.					
Esophageal 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 due to breakdown of an esophageal anastomosis (surgical connection of two separate anatomic structures).					
Fall	Minor with no resultant injuries; intervention not indicated	Symptomatic; noninvasive intervention indicated	Hospitalization indicated	-	-
Definition: A finding of sudden movement downward, usually resulting in injury.					
Fallopian tube anastomotic leak	Asymptomatic; clinical or 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 due to breakdown of a fallopian tube anastomosis (surgical connection of two separate anatomic structures).					
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 diagnostic observations only; intervention not indicated	Symptomatic but non-displaced; immobilization indicated	Severe symptoms; displaced or open wound with bone exposure; disabling; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of traumatic injury to the bone in which the continuity of the bone is broken.					

Injury, poisoning and procedural complications					
	Grade				
Adverse Event	1	2	3	4	5
Gastric 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 due to breakdown of a gastric anastomosis (surgical connection of two separate anatomic structures).					
Gastrointestinal 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 due to breakdown of a gastrointestinal anastomosis (surgical connection of two separate anatomic structures).					
Gastrointestinal stoma necrosis	-	Superficial necrosis; intervention not indicated	Severe symptoms; hospitalization or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of a necrotic process occurring in the gastrointestinal tract stoma.					
Hip fracture	-	Hairline fracture; mild pain; limiting instrumental ADL; non-surgical intervention indicated	Severe pain; hospitalization or intervention indicated for pain control (e.g., traction); operative intervention indicated	Life-threatening consequences; symptoms associated with neurovascular compromise	-
Definition: A finding of traumatic injury to the hip in which the continuity of either the femoral head, femoral neck, intertrochanteric or subtrochanteric regions is broken.					
Injury to carotid artery	-	-	Severe symptoms; limiting self care ADL (e.g., transient cerebral ischemia); repair or revision indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the carotid artery.					
Injury to inferior vena cava	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the inferior vena cava.					
Injury to jugular vein	-	-	Symptomatic limiting self care ADL; disabling; repair or revision indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the jugular vein.					
Injury to superior vena cava	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; repair or revision not indicated	Severe symptoms; limiting self care ADL; disabling; repair or revision indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to the superior vena cava.					
Intestinal stoma 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 contents from an intestinal stoma (surgically created opening on the surface of the body).					
Intestinal stoma obstruction	-	Self-limited; intervention not indicated	Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of blockage of the normal flow of the contents of the intestinal stoma.					
Intestinal stoma 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 leakage from the intestinal stoma.					
Intraoperative arterial 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 an artery during a surgical procedure.					
Intraoperative breast 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

Injury, poisoning and procedural complications					
	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
Definition: A finding of damage to the heart during a surgical procedure.					
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
Definition: A finding of damage to the ear during a surgical procedure.					
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 surgical 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 during 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 surgical procedure.					
Intraoperative hemorrhage	-	-	Postoperative radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of uncontrolled bleeding during a surgical procedure.					
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 biliary tract during a surgical procedure.					
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 the musculoskeletal system during a surgical procedure.					
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
Definition: A finding of damage to the nervous system during a surgical procedure.					
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 procedure.					
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 procedure.					
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; disabling	Life-threatening consequences; urgent intervention indicated	Death

Injury, poisoning and procedural complications					
	Grade				
Adverse Event	1	2	3	4	5
Definition: A finding of damage to the reproductive organs during a surgical procedure.					
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 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 procedure.					
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 the spleen during a surgical procedure.					
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 the urinary system during a surgical procedure.					
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 a vein during a surgical procedure.					
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 kidney anastomosis (surgical connection of two separate anatomic structures).					
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 due to breakdown of an anastomosis (surgical connection of two separate anatomic structures) in the large 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 due to breakdown of a pancreatic anastomosis (surgical connection of two separate anatomic structures).					
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 due to breakdown of a pharyngeal anastomosis (surgical connection of two separate anatomic structures).					
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 occurring after a surgical procedure.					
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 previously undocumented problem that occurs after a thoracic procedure.					
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 surface.					
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 displacement 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 chemotherapeutic agents, for weeks or months following radiotherapy. The inflammatory reaction is confined to the previously irradiated skin and the symptoms disappear after the removal of the pharmaceutical agent.					
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 due to breakdown of a rectal anastomosis (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.					
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 due to breakdown of an anastomosis (surgical connection of two separate anatomic structures) in the small 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 due to breakdown of a spermatic cord anastomosis (surgical connection of two separate anatomic structures).					
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 continuity of a vertebral bone is broken.					
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 (surgically created opening on the surface of the body).					
Stomal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the jejunal mucosal surface close to the anastomosis site following a gastroenterostomy procedure.					
Tracheal hemorrhage	Minimal bleeding identified on clinical or diagnostic 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 trachea.					
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
Definition: A finding of blockage of the lumen of the trachea.					

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 leakage 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
Definition: A finding of leakage due to breakdown of a ureteral anastomosis (surgical connection of two separate anatomic structures).					
Urethral 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 due to breakdown of a urethral anastomosis (surgical connection of two 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 contents from a urostomy.					
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 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 due to breakdown of a uterine anastomosis (surgical connection of two 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
Definition: A disorder characterized by a rupture in the uterine wall.					
Vaginal 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 due to breakdown of a vaginal anastomosis (surgical connection of two separate anatomic structures).					
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 due to breakdown of a vas deferens anastomosis (surgical connection of two separate anatomic structures).					
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
Definition: A finding of a previously undocumented problem related to the vascular access site.					

Injury, poisoning and procedural 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
Definition: A finding of development of a new problem at the site of an existing wound.					
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 dehiscence 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.					
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 broken.					
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	-	-
Definition: An abnormal laboratory test result in which the partial thromboplastin time is found to be greater than the control value. As a possible indicator of coagulopathy, a prolonged partial thromboplastin time (PTT) may occur in a variety of diseases and disorders, both primary and related to treatment.					
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 laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in 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 laboratory test results that indicate an increase in the level of alkaline phosphatase 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 laboratory test results that indicate an 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 laboratory test results that indicate abnormal levels of antidiuretic hormone 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 laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated 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 laboratory test results that indicate an decrease in levels of corticotrophin 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 laboratory test results that indicate abnormal levels of gonadotrophin hormone 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 laboratory test results that indicate abnormal levels of prolactin hormone 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 lung 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 which indicates increased levels of cardiac troponin I in a biological specimen.					
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 biological specimen.					
CD4 lymphocytes decreased	<LLN - 500/mm3; <LLN - 0.5 x 10e9 /L	<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 laboratory test results that indicate an decrease in levels of CD4 lymphocytes 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 laboratory test results that indicate higher than normal levels of cholesterol 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 laboratory test results that indicate an increase in levels of creatine phosphokinase 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 laboratory test results that indicate increased levels of creatinine in a biological 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 computed when the amount of blood ejected during a ventricular contraction of the heart is compared to the amount that was present prior to the contraction.					
Electrocardiogram QT corrected interval prolonged	QTc 450 - 480 ms	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 dysrhythmia characterized by an abnormally long corrected QT interval.					
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 laboratory test results that indicate an decrease in levels of fibrinogen 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 test results that indicate a relative decrease 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 laboratory test results that indicate higher than normal levels of the enzyme gamma-glutamyltransferase in the blood specimen. GGT (gamma-glutamyltransferase) catalyzes the transfer of a gamma glutamyl group from a gamma glutamyl peptide to another peptide, amino acids 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 laboratory test results that indicate abnormal levels of growth hormone in a biological specimen.					
Haptoglobin decreased	<LLN	-	-	-	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of haptoglobin 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 laboratory test results that indicate increased 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 laboratory test results that indicate an increase in the ratio of the patient's prothrombin time to a control sample 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 laboratory test results that indicate an increase in the level of lipase in a biological specimen.					
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9 /L	<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 laboratory test results that indicate a decrease in number of lymphocytes in a blood specimen.					
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	-
Definition: A finding based on laboratory test results that indicate an abnormal increase in the number of lymphocytes in the blood, effusions or bone marrow.					
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<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 laboratory test results that indicate a decrease in number of neutrophils in a blood specimen.					
Pancreatic enzymes decreased	<LLN and asymptomatic	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency	-	-
Definition: A finding based on laboratory test results that indicate an 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/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-
Definition: A finding based on laboratory 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 laboratory test results that indicate an 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 test results that indicate urine production is less relative to previous output.					
Vital capacity abnormal	90 - 75% of predicted value	<75 - 50% of predicted value; limiting instrumental ADL	<50% of predicted value; limiting self care ADL	-	-
Definition: A finding based on pulmonary function test results that indicate an abnormal vital capacity (amount of exhaled after a maximum inhalation) when compared to the predicted value.					
Weight gain	5 - <10% from baseline	10 - <20% from baseline	>=20% from baseline	-	-
Definition: A finding characterized by an increase in overall body weight; for pediatrics, greater than the baseline growth curve.					
Weight loss	5 to <10% from baseline; intervention not indicated	10 - <20% from baseline; nutritional support indicated	>=20% from baseline; tube feeding or TPN indicated	-	-
Definition: A finding characterized by a decrease in overall body weight; for pediatrics, less than the baseline growth curve.					
White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate an decrease in number of white blood cells in a blood specimen.					
Investigations - 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

Metabolism and nutrition disorders					
	Grade				
Adverse Event	1	2	3	4	5
Acidosis	pH <normal, but >=7.3	-	pH <7.3	Life-threatening consequences	Death
Definition: A disorder characterized by abnormally high acidity (high hydrogen-ion concentration) of the blood and other body tissues.					
Alcohol intolerance	-	Present	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in sensitivity to the adverse effects of alcohol, which can include nasal congestion, skin flushes, heart dysrhythmias, nausea, vomiting, indigestion and headaches.					
Alkalosis	pH >normal, but <=7.5	-	pH >7.5	Life-threatening consequences	Death
Definition: A disorder characterized by abnormally high alkalinity (low hydrogen-ion concentration) of the blood and other body tissues.					
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 characterized 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 characterized by excessive loss of water from the body. It is usually caused by severe diarrhea, vomiting or diaphoresis.					
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 characterized by an inability to properly metabolize 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; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of calcium (corrected for albumin) 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 characterized by laboratory test results that indicate an elevation in the concentration of blood sugar. It is usually an indication of diabetes mellitus or glucose intolerance.					
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 characterized by laboratory test results that indicate an elevation in the concentration of potassium in the blood; associated with kidney failure or sometimes with the use of diuretic drugs.					
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 characterized by laboratory test results that indicate an elevation in the concentration of magnesium in the blood.					
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of sodium in the blood.					
Hypertriglyceridemia	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
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of triglyceride concentration in the blood.					
Hyperuricemia	>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
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of uric acid.					
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of albumin in the blood.					

Metabolism and nutrition disorders					
	Grade				
Adverse Event	1	2	3	4	5
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized 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 characterized by laboratory test results that indicate a low concentration of calcium (corrected for albumin) in the blood.					
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<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 characterized by laboratory test results that indicate a low concentration of glucose in the blood.					
Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of potassium in the blood.					
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<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 characterized by laboratory test results that indicate a low concentration of magnesium in the blood.					
Hyponatremia	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of sodium in the blood.					
Hypophosphatemia	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<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 characterized by laboratory test results that indicate a low concentration of phosphates in the blood.					
Iron overload	-	Moderate symptoms; intervention not indicated	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by accumulation of iron in the tissues.					
Obesity	-	BMI 25 - 29.9 kg/m2	BMI 30 - 39.9 kg/m2	BMI >=40 kg/m2	-
Definition: A disorder characterized by having a high amount of body fat.					
Tumor lysis syndrome	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by metabolic abnormalities that result from a spontaneous or therapy-related cytolysis of tumor cells.					
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				
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 characterized by a necrotic process occurring in the soft tissues of the abdominal wall.					
Arthralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in a joint.					
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 characterized by inflammation involving a joint.					
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
Definition: A disorder characterized by necrotic changes in the bone tissue due to interruption of blood supply. Most often affecting the epiphysis of the long bones, the necrotic changes result in the collapse and the destruction of the bone structure.					
Back pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the back region.					
Bone pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the bones.					
Buttock pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the buttocks.					
Chest wall pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation 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 characterized 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 characterized 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 characterized by marked discomfort sensation on the lateral side of the body in the region below the ribs and above 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 characterized by a reduction in the strength of muscles in multiple anatomic sites.					
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	-	-
Definition: A disorder characterized by of stature that is smaller than normal as expected for age.					

Musculoskeletal and connective tissue disorders					
	Grade				
Adverse Event	1	2	3	4	5
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 characterized 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 characterized by excessive fluid in a joint, usually as a result of joint inflammation.					
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 characterized 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 characterized by a decrease in flexibility of a cervical spine joint.					
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 characterized 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 characterized by an abnormal increase in the curvature of the thoracic portion 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 characterized 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 characterized by a reduction in the strength of the muscles on the left side of the 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 characterized by a reduction in the strength of 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 characterized by a reduction in the strength of the muscles on the right side of the body.					
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	-	-
Definition: A disorder characterized by a reduction in the strength of the trunk muscles.					
Muscle weakness upper 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 characterized by a reduction in the strength of the upper limb muscles.					

Musculoskeletal and connective tissue disorders					
	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 characterized by of a malformation of the musculoskeletal system.					
Myalgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation originating from a muscle or group 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 characterized by inflammation involving the skeletal muscles.					
Neck pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the neck area.					
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 characterized 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 characterized 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 characterized by reduced bone mass, with a decrease in cortical thickness and in the number and size of the trabeculae of cancellous bone (but normal chemical composition), resulting in increased fracture incidence.					
Pain in extremity	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the upper or lower extremities.					
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
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the pelvis.					
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 characterized by a malformed, lateral curvature 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 characterized by a necrotic process occurring in the soft tissues of the lower extremity.					
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
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the upper extremity.					

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 characterized 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 characterized by lack of ability to open the mouth 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	Severe length discrepancy >5 cm; limiting self care ADL; disabling; operative intervention indicated	-	-
Definition: A disorder characterized by of a discrepancy between the lengths of the lower or upper extremities.					
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 benign, malignant and unspecified (incl cysts and polyps)					
	Grade				
Adverse Event	1	2	3	4	5
Leukemia secondary to oncology chemotherapy	-	-	-	Present	Death
Definition: A disorder characterized by leukemia arising as a result of the mutagenic effect of chemotherapy agents.					
Myelodysplastic syndrome	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by insufficiently healthy hematapoietic cell production by the bone marrow.					
Treatment related secondary malignancy	-	-	Non life-threatening secondary malignancy	Acute life-threatening secondary malignancy; blast crisis in leukemia	Death
Definition: A disorder characterized by development of a malignancy most probably as a result of treatment for a previously existing malignancy.					
Tumor pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort from a neoplasm that may be pressing on a nerve, blocking blood vessels, inflamed or fractured from metastasis.					
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					
	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 characterized by involvement of the abducens nerve (sixth cranial nerve).					
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 characterized by involvement of the accessory 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 characterized by involvement of the acoustic nerve (eighth cranial nerve).					
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 characterized by an uncomfortable feeling of inner restlessness and inability to stay still; this is a side effect of some psychotropic drugs.					
Amnesia	Mild; transient memory loss	Moderate; short term memory loss; limiting instrumental ADL	Severe; long term memory loss; limiting self care ADL	-	-
Definition: A disorder characterized by systematic and extensive loss of memory.					
Aphonia	-	-	Voicelessness; unable to speak	-	-
Definition: A disorder characterized by the inability to speak. It may result from injuries to the vocal cords or may be functional (psychogenic).					
Arachnoiditis	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the arachnoid membrane and adjacent subarachnoid space.					
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 characterized by lack of coordination of muscle movements resulting in the impairment or inability to perform voluntary 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 characterized by regional paresthesia of the brachial plexus, marked discomfort and muscle weakness, and limited 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 characterized by a necrotic process occurring 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 characterized by loss of cerebrospinal fluid into 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 characterized by a conspicuous change in cognitive 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	-	-
Definition: A disorder characterized by a deterioration in the ability to concentrate.					

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 characterized by a decrease in ability to perceive and respond.					
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 characterized by a disturbing sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking.					
Dysarthria	Mild slurred speech	Moderate impairment of articulation or slurred speech	Severe impairment of articulation or slurred speech	-	-
Definition: A disorder characterized by slow and slurred speech resulting from an inability to coordinate 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 characterized by distortion of sensory perception, 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 characterized by abnormal sensual experience with the taste of foodstuffs; it can 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 characterized by impairment of verbal communication skills, often resulting from brain damage.					
Edema cerebral	-	-	-	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the brain.					
Encephalopathy	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a pathologic process involving the brain.					
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 characterized by abnormal, repetitive, involuntary muscle movements, frenzied speech and extreme restlessness.					
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 characterized by a reduction in the strength 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 characterized by involvement of the facial nerve (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 characterized by involvement of the glossopharyngeal nerve (ninth cranial nerve).					
Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in various parts of the head, not confined to the area of distribution 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 characterized by an abnormal increase of cerebrospinal fluid in the ventricles of the brain.					
Hypersomnia	Mild increased need for sleep	Moderate increased need for sleep	Severe increased need for sleep	-	-
Definition: A disorder characterized 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 diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the hypoglossal 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 characterized by bleeding from the cranium.					
Ischemia cerebrovascular	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	-	-	-
Definition: A disorder characterized by a decrease or absence of blood supply to the brain caused by obstruction (thrombosis or embolism) of an artery resulting in neurological damage.					
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 characterized by involvement of the trochlear nerve (fourth cranial nerve).					
Lethargy	Mild symptoms; reduced alertness and awareness	Moderate symptoms; limiting instrumental ADL	-	-	-
Definition: A disorder characterized by a decrease in consciousness characterized by mental and physical 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 characterized by diffuse reactive astrocytosis with multiple areas of necrotic foci without inflammation.					
Memory impairment	Mild memory impairment	Moderate memory impairment; limiting instrumental ADL	Severe memory impairment; limiting self care ADL	-	-
Definition: A disorder characterized by a deterioration in memory function.					
Meningismus	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by neck stiffness, headache, and photophobia resulting from irritation of the cerebral meninges.					
Movements involuntary	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by uncontrolled and purposeless movements.					
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 characterized by inflammation involving the spinal cord. Symptoms include weakness, paresthesia, sensory loss, marked discomfort and incontinence.					
Neuralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by intense painful sensation along a nerve or group of nerves.					
Nystagmus	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involuntary movements of the eyeballs.					
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 characterized by involvement of the oculomotor nerve (third cranial nerve).					
Olfactory nerve disorder	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the olfactory nerve (first cranial nerve).					

Nervous system disorders					
	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 characterized by functional disturbances of sensory neurons resulting in abnormal cutaneous sensations of tingling, numbness, pressure, cold, and warmth that are experienced in the absence of a stimulus.					
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 characterized by inflammation or degeneration 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 characterized by inflammation or degeneration of the peripheral sensory nerves.					
Phantom pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort related to a limb or an organ that is removed from or is not physically part of the body.					
Presyncope	-	Present (e.g., near fainting)	-	-	-
Definition: A disorder characterized by an episode of lightheadedness and dizziness which may precede an episode of syncope.					
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
Definition: A disorder characterized by dysfunction of the corticospinal (pyramidal) tracts of the spinal cord. Symptoms include an increase in the muscle tone in the lower extremities, hyperreflexia, positive Babinski and a decrease in fine motor coordination.					
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 characterized by inflammation involving a nerve root. Patients experience marked discomfort radiating along a nerve path because of spinal pressure on the connecting nerve root.					
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 characterized by paralysis of the recurrent laryngeal 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
Definition: A disorder characterized by headaches, mental status changes, visual disturbances, and seizures associated with imaging findings of posterior leukoencephalopathy. It has been observed in association with hypertensive encephalopathy, eclampsia, and immunosuppressive and cytotoxic drug treatment. It is an acute or subacute reversible condition.					
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 characterized by a sudden, involuntary skeletal muscular contractions of cerebral or brain stem origin.					
Sinus pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort in the face, between the eyes, or upper teeth 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 characterized 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 by increased involuntary muscle tone that affects the regions interfering with voluntary movement. It results in gait, movement, and speech disturbances.					
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 characterized by a sudden loss of sensory function due to an intracranial vascular event.					
Syncope	-	-	Fainting; orthostatic collapse	-	-
Definition: A disorder characterized by spontaneous loss of consciousness caused by insufficient blood supply to the brain.					

Nervous system disorders					
	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 characterized by a brief attack (less than 24 hours) of cerebral dysfunction of vascular origin, with no persistent neurological deficit.					
Tremor	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by the uncontrolled shaking movement of the whole body or individual 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 characterized by involvement of the trigeminal 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 characterized by involvement of the vagus nerve (tenth cranial nerve).					
Vasovagal reaction	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a sudden drop of the blood pressure, bradycardia, and peripheral vasodilation that may lead to loss of consciousness. It results from an increase in the stimulation of the vagus nerve.					
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

Pregnancy, puerperium and perinatal conditions					
	Grade				
Adverse Event	1	2	3	4	5
Fetal death	-	-	-	-	Fetal loss at any gestational age
Definition: A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without 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 characterized by inhibition of fetal growth resulting 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 characterized by delivery of a viable infant before the normal end of gestation. Typically, viability is achievable between the twentieth and thirty-seventh week of gestation.					
Unintended pregnancy	-	-	Unintended pregnancy	-	-
Definition: A disorder characterized by an unexpected pregnancy at 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; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Psychiatric disorders					
	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
Definition: A disorder characterized by a state of restlessness associated with unpleasant feelings of irritability and tension.					
Anorgasmia	Inability to achieve orgasm not adversely affecting relationship	Inability to achieve orgasm adversely affecting relationship	-	-	-
Definition: A disorder characterized by an inability to achieve orgasm.					
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 characterized by apprehension of danger and dread accompanied by restlessness, tension, tachycardia, and dyspnea unattached to a clearly identifiable stimulus.					
Confusion	Mild disorientation	Moderate disorientation; limiting instrumental ADL	Severe disorientation; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a lack of clear and orderly thought and behavior.					
Delayed orgasm	Delay in achieving orgasm not adversely affecting relationship	Delay in achieving orgasm adversely affecting relationship	-	-	-
Definition: A disorder characterized by sexual dysfunction characterized by a delay in climax.					
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 characterized by the acute and sudden development of confusion, illusions, movement changes, inattentiveness, agitation, and hallucinations. Usually, it is a reversible condition.					
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 characterized by false personal beliefs held contrary to reality, despite contradictory evidence and common sense.					
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 characterized by melancholic feelings of grief or unhappiness.					
Euphoria	Mild mood elevation	Moderate mood elevation	Severe mood elevation (e.g., hypomania)	-	-
Definition: A disorder characterized by an exaggerated feeling of well-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 characterized by a false sensory perception in the absence of an external stimulus.					
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 characterized by difficulty in falling asleep and/or remaining asleep.					
Libido decreased	Decrease in sexual interest not adversely affecting relationship	Decrease in sexual interest adversely affecting relationship	-	-	-
Definition: A disorder characterized 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 characterized 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 characterized by excitement of psychotic proportions manifested by mental and physical hyperactivity, disorganization 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 disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A disorder characterized by a conspicuous change in a 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 characterized by personality change, impaired functioning, and loss of touch with reality. It may be a manifestation of schizophrenia, bipolar disorder or brain tumor.					
Restlessness	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by an inability to rest, relax or be 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 characterized by thoughts of taking one's own 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 characterized by self-inflicted harm in an attempt 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	Creatinine 2 - 3 x above baseline	Creatinine >3 x baseline or >4.0 mg/dL; hospitalization indicated	Life-threatening consequences; dialysis indicated	Death
Definition: A disorder characterized by the acute loss of renal function and is traditionally classified as pre-renal (low blood flow into kidney), renal (kidney damage) and post-renal causes (ureteral or bladder outflow obstruction).					
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 characterized by a rupture in the bladder wall.					
Bladder spasm	Intervention not indicated	Antispasmodics indicated	Hospitalization indicated	-	-
Definition: A disorder characterized by a sudden and involuntary contraction of the bladder wall.					
Chronic kidney disease	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN - 60 ml/min/1.73 m2 or proteinuria 2+ present; urine protein/creatinine >0.5	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 characterized by gradual and usually permanent loss of kidney function resulting 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 characterized by inflammation of the bladder which is not caused by an infection 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 characterized by laboratory test results that indicate blood in the urine.					
Hemoglobinuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characterized by laboratory test results that indicate the presence of free hemoglobin 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 characterized by laboratory test results that indicate the presence of excessive protein in the urine. It is predominantly 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 characterized by the formation of crystals in the 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	-	-
Definition: A disorder characterized by paroxysmal and severe flank marked discomfort radiating to the inguinal area. Often, the cause is the passage of kidney stones.					

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 characterized 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 characterized by an abnormal communication between any part of the urinary system and another organ or anatomic site.					
Urinary frequency	Present	Limiting instrumental ADL; medical management indicated	-	-	-
Definition: A disorder characterized by urination at short intervals.					
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 characterized by inability to control the flow of 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 characterized by accumulation of urine within the bladder because of the inability 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 characterized 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 characterized by a sensation of marked discomfort in the urinary tract.					
Urinary urgency	Present	Limiting instrumental ADL; medical management indicated	-	-	-
Definition: A disorder characterized by a sudden compelling urge to urinate.					
Urine discoloration	Present	-	-	-	-
Definition: A disorder characterized 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

Reproductive system and breast disorders					
	Grade				
Adverse Event	1	2	3	4	5
Azoospermia	-	-	Absence of sperm in ejaculate	-	-
Definition: A disorder characterized by laboratory test results that indicate complete absence of spermatozoa in the semen.					
Breast atrophy	Minimal asymmetry; minimal atrophy	Moderate asymmetry; moderate atrophy	Asymmetry >1/3 of breast volume; severe atrophy	-	-
Definition: A disorder characterized by underdevelopment of the breast.					
Breast pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the breast region.					
Dysmenorrhea	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by abnormally painful abdominal cramps during menses.					
Dyspareunia	Mild discomfort or pain associated with vaginal penetration; discomfort relieved with use of vaginal lubricants or estrogen	Moderate discomfort or pain associated with vaginal penetration; discomfort or pain partially relieved with use of vaginal lubricants or estrogen	Severe discomfort or pain associated with vaginal penetration; discomfort or pain unrelieved by vaginal lubricants or estrogen	-	-
Definition: A disorder characterized by painful or difficult coitus.					
Ejaculation disorder	Diminished ejaculation	Anejaculation or retrograde ejaculation	-	-	-
Definition: A disorder characterized by problems related to ejaculation. This category includes premature, delayed, retrograde and painful ejaculation.					
Erectile dysfunction	Decrease in erectile function (frequency or rigidity of erections) but intervention not indicated (e.g., medication or use of mechanical device, penile pump)	Decrease in erectile function (frequency/rigidity of erections), erectile intervention indicated, (e.g., medication or mechanical devices such as penile pump)	Decrease in erectile function (frequency/rigidity of erections) but erectile intervention not helpful (e.g., medication or mechanical devices such as penile pump); placement of a permanent penile prosthesis indicated (not previously present)	-	-
Definition: A disorder characterized by the persistent or recurrent inability to achieve or to maintain an erection during sexual activity.					
Fallopian tube obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by blockage of the normal flow of the contents in the fallopian tube.					
Fallopian tube stenosis	Asymptomatic clinical or 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 disorder characterized by a narrowing of the fallopian tube lumen.					
Female genital tract 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 characterized by an abnormal communication between a female reproductive system organ and another organ or anatomic site.					
Feminization acquired	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by the development of secondary female sex characteristics in males due to extrinsic factors.					
Genital edema	Mild 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	Lymphorrhea; gross deviation from normal anatomic contour; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the genitals.					
Gynecomastia	Asymptomatic breast enlargement	Symptomatic (e.g., pain or psychosocial impact)	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by excessive development of the breasts in males.					
Hematosalpinx	Minimal bleeding identified on imaging study or laparoscopy; 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

Reproductive system and breast disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A disorder characterized by the presence of blood in a fallopian tube.					
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 characterized by irregular cycle or duration of menses.					
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 characterized by disturbances of milk secretion. It is not necessarily related to pregnancy that is observed in females and can be observed in males.					
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 characterized by abnormally heavy vaginal bleeding 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 characterized 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 characterized 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 characterized 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 characterized by tearing or disruption of the ovarian tissue.					
Ovulation pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in one side of the abdomen between menstrual cycles, around the time of the discharge of the ovum from the ovarian follicle.					
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 characterized by a reduction in the strength of the muscles of the pelvic floor.					
Pelvic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the pelvis.					
Penile pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the penis.					
Perineal 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 area between the genital organs and the anus.					
Premature menopause	-	-	Present	-	-
Definition: A disorder characterized by ovarian failure before the age of 40. Symptoms include hot flashes, 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

Reproductive system and breast disorders					
	Grade				
Adverse Event	1	2	3	4	5
Definition: A disorder characterized by bleeding from the prostate gland.					
Prostatic obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by compression of the urethra secondary to enlargement of the prostate gland. This results in voiding difficulties (straining to void, slow urine stream, and incomplete emptying of the bladder).					
Prostatic 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 prostate gland.					
Scrotal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation 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 characterized 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 characterized by blockage of the normal flow of the contents of the spermatic cord.					
Testicular disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic but not interfering with urination or sexual activities; intervention not indicated; limiting instrumental ADL	Severe symptoms; interfering with urination or sexual function; limiting self care ADL; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by involvement of the testis.					
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 characterized by bleeding from the testis.					
Testicular 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 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 characterized by an abnormal communication 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 characterized 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 characterized by blockage of the uterine outlet.					
Uterine 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 uterus.					
Vaginal discharge	Mild vaginal discharge (greater than baseline for patient)	Moderate to heavy vaginal discharge; use of perineal pad or tampon indicated	-	-	-
Definition: A disorder characterized by vaginal secretions. Mucus produced by the cervical glands is discharged from the vagina naturally, especially during the childbearing years.					
Vaginal dryness	Mild vaginal dryness not interfering with sexual function	Moderate vaginal dryness interfering with sexual function or causing frequent discomfort	Severe vaginal dryness resulting in dyspareunia or severe discomfort	-	-
Definition: A disorder characterized by an uncomfortable feeling of itching and burning in the vagina.					

Reproductive system and breast 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 characterized 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 characterized 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 characterized by inflammation involving the vagina. Symptoms may include redness, edema, marked discomfort and an increase in vaginal discharge.					
Vaginal obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by blockage of vaginal canal.					
Vaginal 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 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 characterized 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 characterized by a narrowing of the vaginal canal.					
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 characterized by involuntary spasms of the pelvic floor muscles, resulting in pathologic tightness of the vaginal wall during penetration such as during sexual intercourse.					
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

Respiratory, thoracic and mediastinal 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 characterized by progressive and life-threatening pulmonary distress in the absence of an underlying pulmonary condition, usually following major trauma or surgery.					
Allergic rhinitis	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by an inflammation of the nasal mucous membranes caused by an IgE-mediated response to external allergens. The inflammation may also involve the mucous membranes of the sinuses, eyes, middle ear, and pharynx. Symptoms include sneezing, nasal congestion, rhinorrhea and itching.					
Apnea	-	-	Present; medical intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by cessation of breathing.					
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 characterized by inhalation of solids or liquids into the lungs.					
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 characterized by the collapse of part or the entire lung.					
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 characterized by an abnormal communication between the bronchus and another 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 characterized by blockage of a bronchus passage, most often by bronchial secretions 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
Definition: A disorder characterized by a narrowing of the bronchial tube.					
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 characterized by an abnormal communication between a bronchus and the pleural cavity.					
Bronchopulmonary 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 characterized by bleeding from the bronchial wall and/or lung parenchyma.					

Respiratory, thoracic and mediastinal disorders					
	Grade				
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 characterized by a sudden contraction of the smooth muscles of the bronchial wall.					
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 characterized by milky pleural effusion (abnormal collection of fluid) resulting from 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 characterized by sudden, often repetitive, spasmodic contraction of the thoracic cavity, resulting in violent release of air from the lungs and usually accompanied by a distinctive sound.					
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 characterized 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 characterized 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 characterized by repeated gulp sounds that result from an involuntary opening and closing of the glottis. This is attributed to a spasm of the diaphragm.					
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 characterized by harsh and raspy voice arising 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
Definition: A disorder characterized by a decrease in the level of oxygen in the body.					
Laryngeal 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
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the larynx.					
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 characterized 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 characterized by bleeding from the larynx.					
Laryngeal inflammation	Mild sore throat; raspy voice	Moderate sore throat; analgesics indicated	Severe throat pain; endoscopic intervention indicated	-	-
Definition: A disorder characterized by an inflammation involving the larynx.					

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 characterized by an inflammation involving the mucous membrane of the larynx.					
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 characterized by blockage of the laryngeal airway.					
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
Definition: A disorder characterized by a narrowing of the laryngeal airway.					
Laryngopharyngeal dysesthesia	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 characterized by an uncomfortable persistent sensation in the area of the laryngopharynx.					
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 characterized by paroxysmal spasmodic muscular contraction of the vocal cords.					
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 characterized by bleeding from the mediastinum.					
Nasal congestion	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Associated with bloody nasal discharge or epistaxis	-	-
Definition: A disorder characterized by obstruction of the nasal passage due to mucosal edema.					
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 characterized by an abnormal communication between the pharynx and another organ or anatomic site.					
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 characterized by bleeding from the pharynx.					
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 characterized by an inflammation involving the mucous membrane of the pharynx.					
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 characterized 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 characterized by a narrowing of the pharyngeal airway.					
Pharyngolaryngeal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation 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	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by an increase in amounts of fluid within the pleural cavity. Symptoms include shortness of breath, cough and marked chest discomfort.					
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 characterized by bleeding from the pleural cavity.					
Pleuritic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the pleura.					
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
Definition: A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma.					
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 characterized 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 characterized by excessive mucous secretion in the back of the nasal cavity or throat, causing sore throat and/or coughing.					
Productive cough	Occasional/minimal production of sputum with cough	Moderate sputum production; limiting instrumental ADL	Persistent or copious production of sputum; limiting self care ADL	-	-
Definition: A disorder characterized by expectorated secretions upon coughing.					
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 characterized by accumulation of fluid in the lung tissues that causes a disturbance 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 characterized by the replacement of the lung tissue by connective tissue, leading to progressive dyspnea, respiratory 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

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Definition: A disorder characterized by an abnormal communication between the lung and another organ 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 characterized by an increase in pressure within 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 characterized by impaired gas exchange by the respiratory system resulting in hypoxemia and a decrease in oxygenation of the tissues that may be associated with an increase in arterial levels of carbon dioxide.					
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 characterized by weight gain, dyspnea, pleural and pericardial effusions, leukocytosis and/or renal failure originally described in patients treated with all-trans retinoic acid.					
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 characterized by involvement of the paranasal 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 characterized by cessation of breathing for short periods during sleep.					
Sneezing	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized 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 characterized 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 characterized by a high pitched breathing sound due to laryngeal or upper airway 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 characterized by an abnormal communication between the trachea and another 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
Definition: A disorder characterized by an inflammation involving the mucous membrane of the trachea.					
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 characterized by a narrowing of the trachea.					

Respiratory, thoracic and mediastinal 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 characterized by a change in the sound and/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 characterized by a high-pitched, whistling sound during breathing. It results from the narrowing or obstruction of the 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 cover the hair loss but it does not require a wig or hair piece to camouflage	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; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by a decrease in density of hair compared to normal for a given individual 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 characterized by an abnormal body smell resulting from the growth of bacteria on the body.					
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 characterized by inflammation of the skin characterized by the presence of bullae which are filled with fluid.					
Dry 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 characterized 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 characterized by target lesions (a pink-red ring around a pale center).					
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 characterized by generalized inflammatory erythema and exfoliation. The inflammatory process involves > 90% of 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	-	-
Definition: A disorder characterized by shrinking of adipose tissue.					
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 characterized by the presence of excess hair growth in women in anatomic sites where growth is considered to be a secondary male characteristic and under androgen control (beard, moustache, chest, abdomen)					
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	-	-
Definition: A disorder characterized by excessive perspiration.					

Skin and subcutaneous tissue disorders					
	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 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 destructive means of hair removal to camouflage; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by hair density or length beyond the accepted limits of normal in a particular body region, for a particular age or race.					
Hypohidrosis	-	Symptomatic; limiting instrumental ADL	Increase in body temperature; limiting self care ADL	Heat stroke	Death
Definition: A disorder characterized by reduced sweating.					
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 characterized by hypertrophy of the subcutaneous adipose tissue at the site of multiple subcutaneous injections of insulin.					
Nail discoloration	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characterized by a change in the color of the nail plate.					
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 characterized by loss of all or a portion of the nail.					
Nail ridging	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characterized 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 characterized by marked discomfort sensation in the skin.					
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	-	-
Definition: A disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of the hands or the soles of the feet.					
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 characterized by swelling due to an excessive 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
Definition: A disorder characterized by an increase in sensitivity of the skin to light.					

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 characterized 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	-	-
Definition: A disorder characterized by hemorrhagic areas of the skin and mucous membrane. Newer lesions appear reddish in color. Older lesions are usually a darker purple color and eventually become a brownish-yellow 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; life-threatening consequences	Death
Definition: A disorder characterized by an eruption of papules and pustules, typically appearing in face, 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	-	-
Definition: A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbillform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and associated with pruritus.					
Scalp pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation 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 characterized by the degeneration and thinning of the epidermis and dermis.					
Skin hyperpigmentation	Hyperpigmentation covering <10% BSA; no psychosocial impact	Hyperpigmentation covering >10% BSA; associated psychosocial impact	-	-	-
Definition: A disorder characterized 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 characterized 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 characterized by an area of hardness in the skin.					
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
Definition: A disorder characterized by circumscribed, inflammatory and necrotic erosive lesion on the skin.					

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 characterized by less than 10% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.					
Telangiectasia	Telangiectasias covering <10% BSA	Telangiectasias covering >10% BSA; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by local dilatation of small vessels resulting in red discoloration of 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 characterized by greater than 30% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the 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 at age 40 - 45 years of age	Menopause occurring before age 40 years of age	-	-
Definition: A disorder characterized by the permanent cessation of menses, usually defined by 12 consecutive months of amenorrhea in 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 procedures - 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

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
Definition: A disorder characterized by leakage of intravascular fluids into the extravascular space. This syndrome is observed in patients who demonstrate a state of generalized leaky capillaries following shock syndromes, low-flow states, ischemia-reperfusion injuries, toxemias, medications, or poisoning. It can lead to generalized edema and multiple organ 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 characterized by episodic reddening of the face.					
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 characterized by a localized collection of blood, usually clotted, in an organ, space, or tissue, due to a break in the 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 characterized by an uncomfortable and temporary sensation of intense body warmth, flushing, sometimes accompanied 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 WNL; monotherapy indicated Pediatric: recurrent or persistent (>=24 hrs) BP >ULN; monotherapy indicated	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 characterized by a pathological increase in blood pressure; a repeatedly elevation in the blood pressure exceeding 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 characterized by a blood pressure that is below the normal expected for an individual 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
Definition: A disorder characterized by the loss of lymph fluid into the surrounding tissue or body cavity.					
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 characterized 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 characterized by a cystic lesion containing lymph.					
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 characterized by impaired circulation to an extremity.					
Phlebitis	-	Present	-	-	-
Definition: A disorder characterized by inflammation of the wall of a vein.					
Superficial thrombophlebitis	-	Present	-	-	-
Definition: A disorder characterized by a blood clot and inflammation involving a superficial vein of the extremities.					

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 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 characterized by occlusion of a vessel by a thrombus 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 characterized by inflammation involving the wall 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 characterized 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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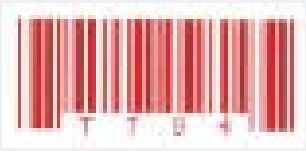

Appendix B: Pemphigus Disease Area Index (PDAI)

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 > 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	**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 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 membrane

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	

Total Activity Score: ☐ **Total Damage Score** ☐

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 Wallace House 17-21 Maxwell Place Stirling, Scotland FK81JU Mobile Phone: PPD Office Phone: PPD ext. PPD
Original Protocol:	19 December 2016
Amendment 1.1	18 January 2017
Amendment 2.0	12 April 2017
Amendment 3.0	10 October 2017

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/m^2
- 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.

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.

Section, Page Number	Original Text	Revised Text	Rationale
Cover, page 1	Blythe Thomson, MD 43 Thorn[redacted]reet, Cambridg[redacted] 01240	Richard Kay, MD Wallace House 17-21 Maxwell Place Stirling, Scotland FK81JU Mobile Phone: (+44) 7747 621 827 Office Phone: (+44) 1786 460 400 ext. 24461	Medical Monitor information updated
Eme[redacted]cy Contact Infor[redacted]tion, page 3	Bly[redacted]om , MD b.t[redacted]@medpace.com Mc[redacted]one: 1-513-748-2122 [redacted]ne: 1-[redacted]-579-9911 ext.	Richard Kay, MD r.kay@medpace.com Mobile phone: (+44) 7747 621 827 Office phone: (+44) 1786 460 400 ext. 24461	Medical Monitor information updated
Synopsis, Exploratory Objectives, page 7		• *Exploratory biomarkers to investigate immune response associated with pemphigus*	Added an additional exploratory objective to investigate other possible biomarkers associated with the pemphigus immune response
Synopsis, Diagnosis and main entry criteria, page 9	c. If bein[redacted]d with corticosteroids, dose m[redacted]mg/kg/day and stable (< 10 [redacted]n dose) for 2 weeks pri[redacted]g	c. If being treated with corticosteroids, dose must be ≤ 1mg/kg/day *of prednisone or equivalent* and stable (< 10% change in dose) for 2 weeks prior to screening	Clarification of allowable corticosteroids
Syno[redacted]s, Diagnosis and [redacted]entry crite[redacted]page 9	5. [redacted]ass index (BMI) 18.5 – 35.0 kg/[redacted]	5. Body mass index (BMI) 18.5 – *39.9*~~35.0~~ kg/m^2;	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
Syno[redacted]s, Diagnosis and main entry criteria, page 9	6. [redacted]egativ[redacted]rine pregnancy test (for women of childbearing potential) documented prior to the first dose of study drug;	6 Has a negative ~~urine~~ pregnancy test (for women of childbearing potential) documented prior to the first dose of study drug;	Allows for serum or urine tests as per institutional standards
Synopsis, Diagnosis and main entry criteria, page 10	10. Cellular therapy at any time prior to screening	10. Cellular therapy*, including CAR-T,* therapy at any time prior to screening	To further clarify the restriction on all cellular therapy

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 Number	Original Text	Revised Text	Rationale
Pharmacodynamics/ Activity, page 13	PD samples will be collected for analysis of IgG (serial assessment of IgG levels to identify Cmin, Tmin); 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 (FCGR2A SNP, RNAseq, urine IgG, CD3+CD4+ T, CD3+CD8+ T, monocytes, NK cells and B cells).	PD samples will be collected for analysis of IgG (serial assessment of IgG levels to identify Cmin, Tmin); 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 (FCGR2A 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.*	Added an additional exploratory objective to investigate other possible biomarkers associated with the pemphigus immune response
Synopsis, Skin Biopsy, page 13	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 *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.	Clarifies type of skin the optional biopsies may be taken from
Criteria for Evaluation, page 14		• *Exploratory biomarkers to investigate immune response associated with pemphigus*	Added an additional exploratory objective to investigate other possible biomarkers associated with the pemphigus immune response
Table 1, Study Assessments, page 16		*Pemphigus immune response biomarkers*	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
Table 1, Study Assessments, page 16	FCGR2A^{m}	FCGR2A^{m} *by buccal swab*	Clarifies method of sample collection
Table 1, Study Assessments, page 17	m: Samples to be collected and stored; pending review of clinical and pharmacodynamics assessments	m: *Buccal* ~~S~~samples to be collected and stored; pending review of clinical and pharmacodynamics assessments	Clarifies method of sample collection

Section, Page Number	Original Text	Revised Text	Rationale
Section 2.2, Selection of Doses in this Study, page 27	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.	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~~	Clarifies that no treatment was given for the Grade 2 AE of headache in the Phase 1a study.
Section 3.3, Exploratory Objectives, Page 29		o *Exploratory biomarkers to investigate immune response associated with pemphigus*	Added an additional exploratory objective to investigate other possible biomarkers associated with the pemphigus immune response
Section 4.2, Exploratory Outcome Measures, page 31		• *Exploratory biomarkers to investigate immune response associated with pemphigus*	Added an additional exploratory objective to investigate other possible biomarkers associated with the pemphigus immune response
Section 5.2, Inclusion Criteria, page 34	c. If being treated with corticosteroids, dose must be ≤ 1mg/kg/day and stable (< 10% change in dose) for 2 weeks prior to screening	c. If being treated with corticosteroids, dose must be ≤ 1mg/kg/day *of prednisone or equivalent* and stable (< 10% change in dose) for 2 weeks prior to screening	Clarification of allowable corticosteroids
Section 5.2, Inclusion Criteria, page 35	5. Body mass index (BMI) 18.5 – 35.0 kg/m2;	5. Body mass index (BMI) 18.5 – *39.9*~~35.0~~ kg/m2;	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
Section 5.2, Inclusion Criteria, page 35	6. Has a negative urine pregnancy test (for women of childbearing potential) documented prior to the first dose of study drug;	6. Has a negative ~~urine~~ pregnancy test (for women of childbearing potential) documented prior to the first dose of study drug;	Allows for serum or urine tests as per institutional standards
Section 5.3, Exclusion Criteria, page 36	10. Cellular therapy at any time prior to screening	10. Cellular therapy*, including CAR-T,* at any time prior to screening	To further clarify the restriction on all cellular therapy

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 *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	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

Section, Page Number	Original Text	Revised Text	Rationale
Section 7.7, Dose 2 Follow-up Day 12, page 49		• *Exploratory pemphigus immune response biomarkers*	Added an additional exploratory objective to investigate other possible biomarkers associated with the pemphigus immune response
Section 7.8, Treatment Day 14 (Dose 3), page 50		• *Exploratory pemphigus immune response biomarkers*	Added an additional exploratory objective to investigate other possible biomarkers associated with the pemphigus immune response
Section 7.9, Dose 3 Follow-up Day 19, page 51		• *Exploratory pemphigus immune response biomarkers*	Added an additional exploratory objective to investigate other possible biomarkers associated with the pemphigus immune response
Section 7.10, Treatment Day 21 (Dose 4), page 51		• *Exploratory pemphigus immune response biomarkers*	Added an additional exploratory objective to investigate other possible biomarkers associated with the pemphigus immune response
Section 7.11, Treatment Day 28 (Dose 5), page 52		• *Exploratory pemphigus immune response biomarkers*	Added an additional exploratory objective to investigate other possible biomarkers associated with the pemphigus immune response
Section 7.14, Follow-up Day 33, page 54		• *Exploratory pemphigus immune response biomarkers*	Added an additional exploratory objective to investigate other possible biomarkers associated with the pemphigus immune response
Section 7.15, Follow-up Day 42, page 55		• *Exploratory pemphigus immune response biomarkers*	Added an additional exploratory objective to investigate other possible biomarkers associated with the pemphigus immune response
Section 7.16, Follow-up Day 56, page 56		• *Exploratory pemphigus immune response biomarkers*	Added an additional exploratory objective to investigate other possible biomarkers associated with the pemphigus immune response
Section 7.17, Follow-up Day 84, page 56		• *Exploratory pemphigus immune response biomarkers*	Added an additional exploratory objective to investigate other possible biomarkers associated with the pemphigus immune response
Section 7.18, Follow-up Day 112, page 57		• *Exploratory pemphigus immune response biomarkers*	Added an additional exploratory objective to investigate other possible biomarkers associated with the pemphigus immune response

Section, Page Number	Original Text	Revised Text	Rationale
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 weight will be limited to~~ *is* 111 kg.	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.

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 *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~~s 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).	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 Number	Original Text	Revised Text	Rationale
Section 9.6.1, Figure 1, last box, page 64	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	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.*	Provision of a maximum duration of infusion in accordance with the requirements for SYNT001 preparation and administration as outlined in the pharmacy manual.

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 sponso [redacted] the F [redacted] ~~the IRBs~~ as soo [redacted] po [redacted] le [redacted] ve [redacted] ater tha [redacted] ca [redacted] th [redacted] spo [redacted] 's [redacted] n o [redacted] eve [redacted] Th [redacted] rm [redacted] sti [redacted]	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 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).	[redacted] , S [redacted] *or* [redacted] - [redacted] ~~xpe~~ [redacted] ~~d (a~~ [redacted] ~~sev~~ [redacted] erienced b [redacted] he s [redacted] e [redacted] rmed consent th [redacted] he last study [redacted] t, regardless of r [redacted] hip to study drug, must be promptly reported (within 24 hours of the Investigator becoming aw [redacted] nt) by tele [redacted] ne [redacted] sm [redacted] on to the [redacted] nsc [redacted]	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.
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 [redacted] l S [redacted] K [redacted] M [redacted]): [redacted]) 1 [redacted] nsi [redacted] 244 [redacted] bile phone [redacted] 44) [redacted] 1 827 [redacted] ail: r.kay@medp [redacted]	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	[redacted] ~~nsor Contact: Ry~~ [redacted] ~~robino~~ ~~SVP Clinical Operations and Data Management~~ ~~Phone: 617-913-1681~~ ~~Email: ryan@syntimmune.com~~	Sponsor contact information updated

Section, Page Number	Original Text	Revised Text	Rationale
Section 14, dy Administra , Table 6, pa 6	Sponsor Medical Director: Laurence Blumberg, MD Founder and Chief Operating Officer Phone: 917-4 -22 Email: laur nti ne.com	Sponsor *Contact and* Medical Director: Laurence Blumberg, MD President and Chief Operating Officer Phone: 917-415-2210 Email: laur@syntimmune.com	Sponsor contact information updated
Section Admini Table 6	Blythe Thom Medpace 43 Thorndike ee Cambridge, 01 Phone: 513-5 99 xt.27201 Email: b.thoms medpace.com	Richard Kay, MD Medpace Wallace House 17-21 Maxwell Place Stirling, Scotland FK81JU Phone: (+44) 1786 460 400 extension 24461 Email: r.kay@medpace.com	Medical Monitor information updated

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

Sponsor Medical Director:	Laurence Blumberg, MD Founder and Chief Operating Officer PPD 917-415-2210 laur@syntimmune.com

Revised T

Table 2 : St istrative Stru

Sponsor	~~ce Blumberg, MD~~ *John Humphries, MD* ~~er and Chief Operating Officer~~ *Medical* *r* ~~917-415-2210~~ *1-434-270-4827* ~~laur@syntimmune.com~~ *jhumphries@biologicsconsulting.com*

Rationale: Provides current contact information for medical inquiries.

Sincerely,

Stephanie Haller

Stephanie Haller
Vice President, Clinical Operations
Syntimmune, Inc.

PPD

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:	PPD 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
Amendment 4.0	8 June 2018

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 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 once-weekly 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

	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)	The evaluation of corticosteroid use during the study will be summarized by cohort and timepoint
	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 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[c]	≤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[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 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.

Study population	Male or female subjects aged 18 and older with pemphigus (vulgaris or foliaceus) in active stage
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 (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 [≤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/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.
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, and administration	**Study drug:** SYNT001 **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

<table>
<tr><td>Control, dose, and route of administration</td><td>Not applicable</td></tr>
<tr><td>Duration of subject participation</td><td>The duration of subject participation for each cohort is as follows:
<table>
<tr><th rowspan="2">Cohort[a]</th><th rowspan="2">Screening</th><th rowspan="2">Treatment</th><th rowspan="2">Follow-up</th><th colspan="2">Maximum Total</th></tr>
<tr><th>Days</th><th>Weeks</th></tr>
<tr><td>1</td><td>≤14 days</td><td>28 days</td><td>84 days</td><td>126 days</td><td>18 weeks</td></tr>
<tr><td>2</td><td>≤14 days</td><td>28 days</td><td>84 days</td><td>126 days</td><td>18 weeks</td></tr>
<tr><td>3</td><td>≤14 days</td><td>91 days</td><td>84 days</td><td>189 days</td><td>27 weeks</td></tr>
</table>
a. Planned dose and duration of subject participation for Cohort 4 (optional cohort) will be determined following DEC data review. All available data will be considered.</td></tr>
<tr><td>Permitted and prohibited concomitant treatments</td><td>All treatments a subject receives within 14 days prior to enrollment through the end of the study will be documented.
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, histamine$_2$ (H_2) 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.
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</td></tr>
</table>

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

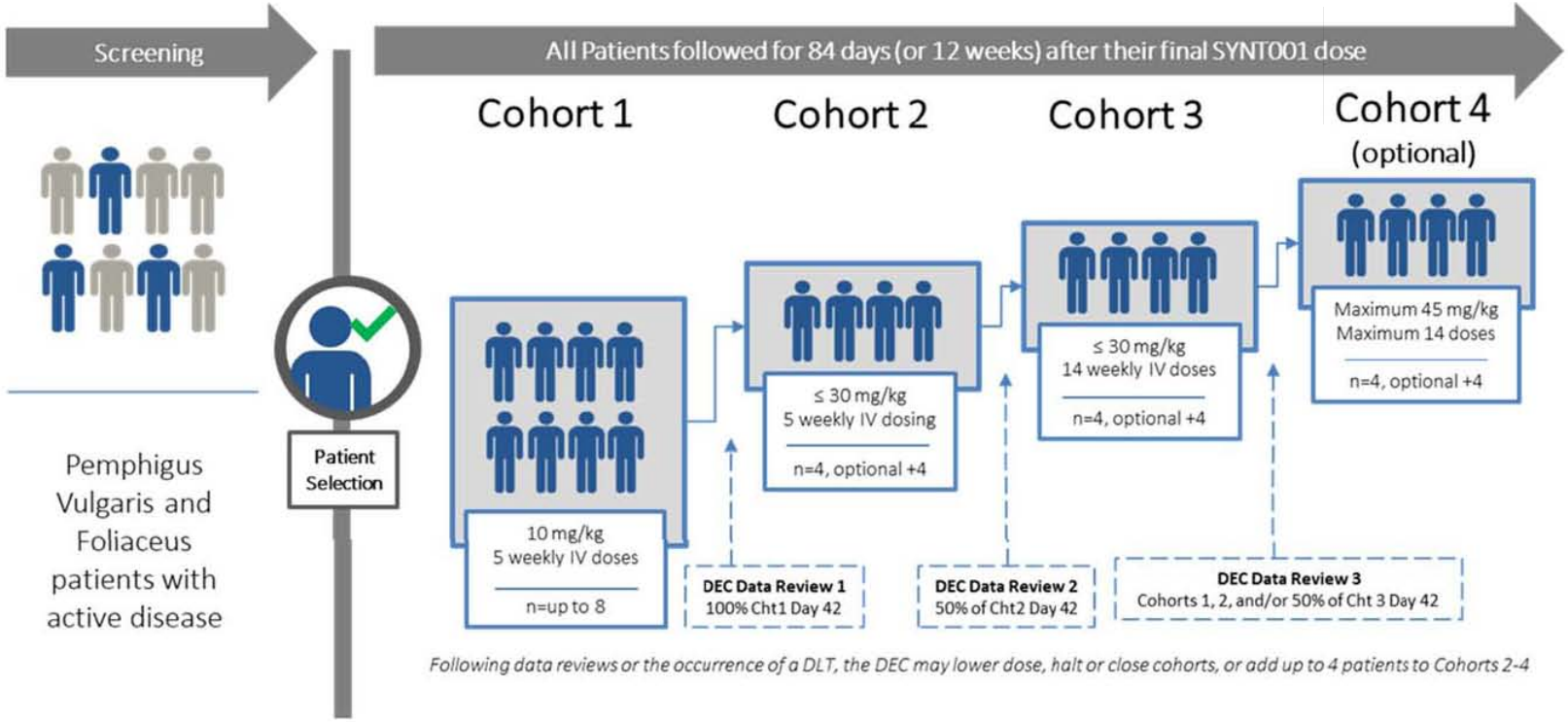

Table 2. Study Assessments for Cohort 1

	Screening	Treatment Period															Follow-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 (±1 h)**	**2 (±2 h)**	**5[p] (±4 h)**	**7 (±6 h)**	**12[p] (±6 h)**	**14 (±6 h)**	**19[p] (±6 h)**	**21 (±6 h)**	**28 (±6 h)**	**29 (±1 h)**	**30 (±2 h)**	**33 (±4 h)**	**42 (±3 d)**	**56 (±5 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
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	X[q]
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[l]		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 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 = 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.

l. **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	Treatment Period					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)[l]	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
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; 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.

l. **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	Treatment Period														Follow-Up				
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 administration[k]		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	*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 = 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.

l. **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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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
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
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 plasma concentration determined directly from the concentration-time profile
CRO	contract research organization
CV	coefficient of variation
CVID	common variable immune deficiency
D5W	dextrose 5% in water
DEC	Dose Escalation Committee
DIF	direct immunofluorescence
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
Dsg	desmoglein
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	$histamine_2$
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 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 antigen-presenting 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

(AEs), treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) summarized by cohort, severity, and relationship to study product

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 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 ($time_0$) 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
- 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 ± 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 (2ºC to 8ºC/36ºF to 46ºF) 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[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[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 [≤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/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**
• 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, 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 (≥25) (Shimizu et al., 2014). The Investigator will determine a PDAI score as follows: 0 to 250 points for disease activity (≤120 for skin, ≤10 for scalp, and ≤120 for mucosa), and 0 to 13 points for damage (≤12 for skin and ≤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 ± 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, histamine$_2$ (H_2) 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.

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 ± 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 ± 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 ± 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 (± 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 (± 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 (± 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 (± 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 (± 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 (± 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 ± 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 ± 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 ± 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 (± 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 (± 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 (± 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 (± 1 day) and Cohort 3 Days 7, 14, 21, 28, 35, 49, 56, 63, 70, 77, and 84 (± 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)
- 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 (± 1 day) and Cohort 3 Days 42 and 91 (± 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 (± 1 day) and 56 (± 3 days) and Cohort 3 Days 98 (± 1 day) and 119 (± 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 (± 1 day) and 84 (± 5 days) and Cohort 3 Days 105 (± 1 day) and 147 (± 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 (± 5 days) and Cohort 3 Day 175 (± 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.

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)
    - 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, 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**
- **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:

Medpace Clinical Safety
Medpace SAE hotline:
Telephone: PPD dial P or PPD dial P
Facsimile: PPD or PPD
e-mail: PPD

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

Medical Safety Contact

PPD
Phone (EU): PPD extension PPD
Mobile phone: PPD
Email: PPD

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

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

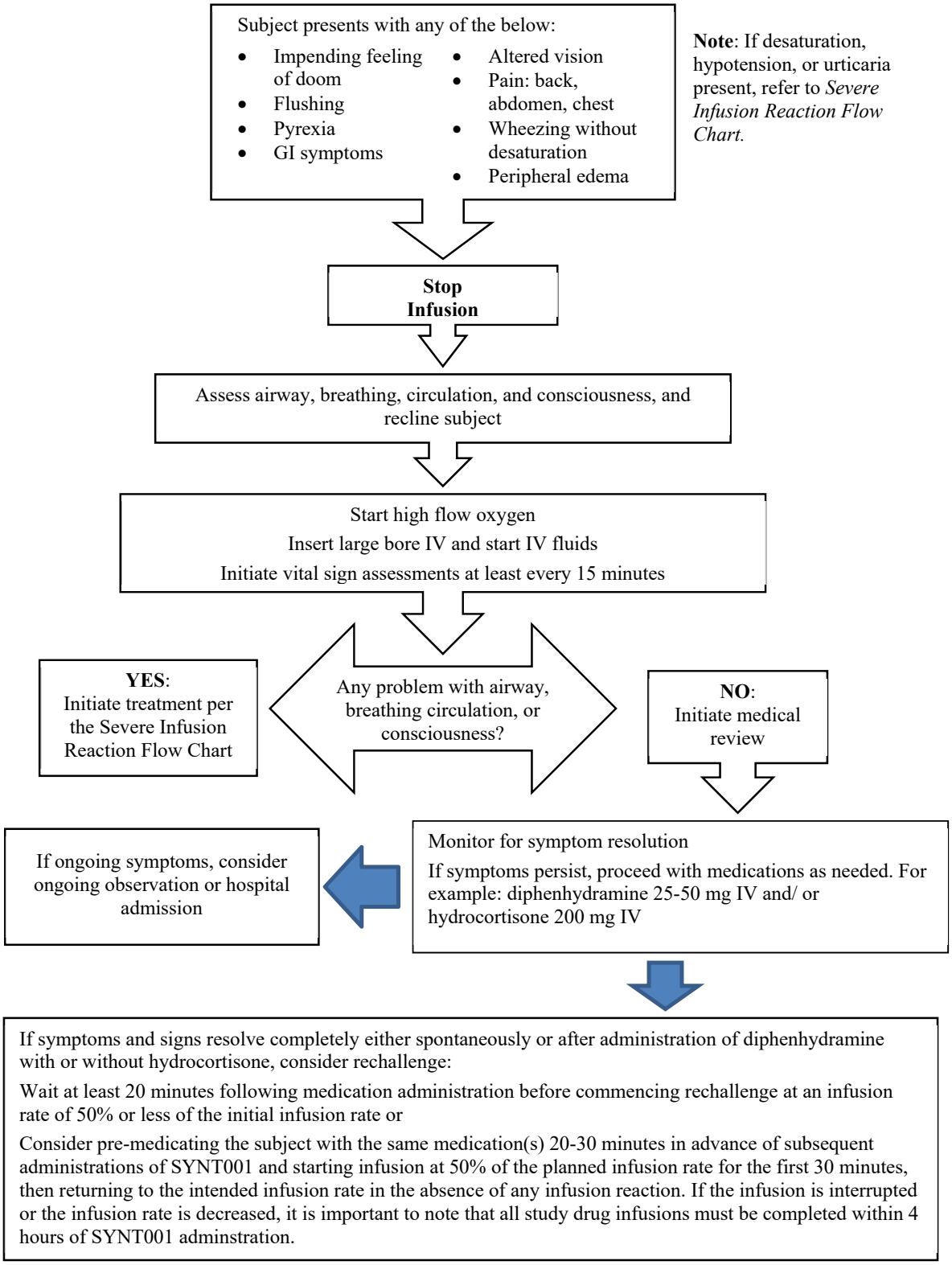

Figure 3. Management of Severe (Grade 3 or Higher) Infusion Reactions

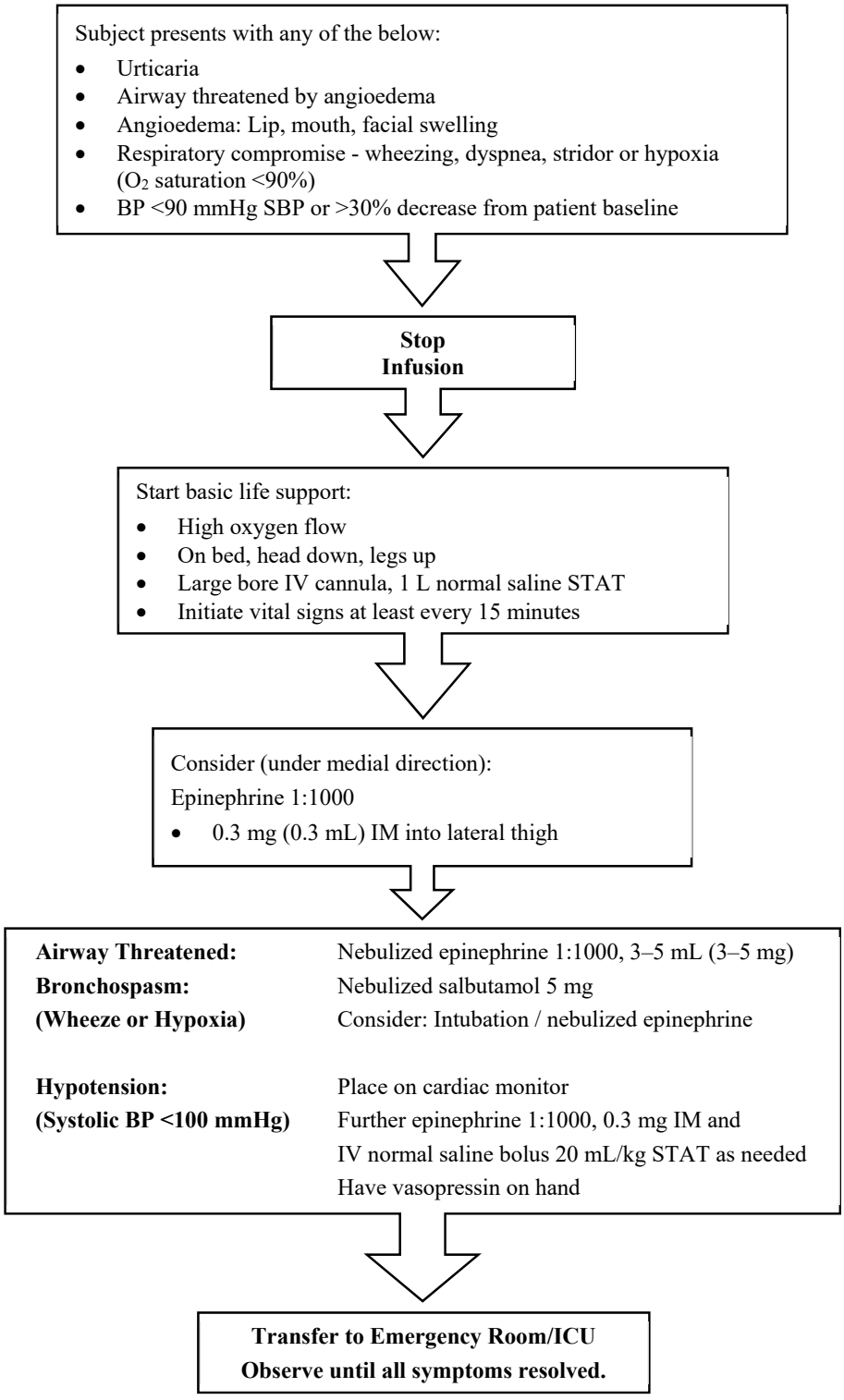

Table 9. Grading and Management of Allergic or Infusion-Related Reactions

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 (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-γ, 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.

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.

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 ≥60% and ≤90% from baseline and (ii) a PDAI total activity score of ≥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 AUC_{0-24} and $AUC_{0-\infty}$ 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 $\log_{10}$ 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.

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.

Table 10. Study Administrative Structure

Sponsor Contact and Medical Director:	PPD PPD Phone: PPD Email: PPD
Medical Monitor:	PPD Medpace Wallace House Stirling, Scotland FK81JU Phone: PPD extension PPD Email: PPD
Study Monitoring:	Medpace 5375 Medpace Way Cincinnati, OH 45227 USA Phone (Main): PPD Email: PPD

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

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

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 *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 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).

CONTENTS

Blood and lymphatic system disorders					
	Grade				
Adverse Event	1	2	3	4	5
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	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
Definition: A disorder characterized by an reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.					
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 characterized by the inability of the bone marrow to produce hematopoietic elements.					
Disseminated intravascular coagulation	-	Laboratory findings with no bleeding	Laboratory findings and bleeding	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by systemic pathological activation of blood clotting mechanisms which results in clot formation throughout the body. There is an increase in the risk of hemorrhage as the body is depleted of platelets and coagulation factors.					
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 characterized by an ANC <1000/mm3 and 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.					
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 characterized by laboratory test results that indicate widespread erythrocyte cell 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 characterized by a form of thrombotic microangiopathy with renal failure, hemolytic anemia, and severe thrombocytopenia.					
Leukocytosis	-	-	>100,000/mm3	Clinical manifestations of leucostasis; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate an increased number of white blood cells in the blood.					
Lymph node 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 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 spleen.					
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
Definition: A disorder characterized by the presence of microangiopathic hemolytic anemia, thrombocytopenic purpura, fever, renal abnormalities and neurological abnormalities such as seizures, hemiplegia, and visual disturbances. It is an acute or subacute condition.					
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
Definition: A disorder characterized by signs and symptoms related to acute ischemia of the myocardium secondary to coronary artery disease. The clinical presentation covers a spectrum of heart diseases from unstable angina to myocardial infarction.					
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 characterized by a defect in aortic valve function or structure.					
Asystole	Periods of asystole; non-urgent medical management indicated	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia without cardiac electrical activity. Typically, this is accompanied by cessation of the 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 characterized by a dysrhythmia without discernible P waves and an irregular ventricular response due to multiple reentry circuits. The rhythm disturbance originates above the ventricles.					
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 characterized by a dysrhythmia with organized rhythmic atrial contractions with a rate of 200-300 beats per minute. The rhythm disturbance originates in the atria.					
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 characterized by a dysrhythmia with complete 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	-	-	-
Definition: A disorder characterized by a dysrhythmia with a delay in the time required for the conduction of an electrical impulse through the atrioventricular (AV) node beyond 0.2 seconds; prolongation of the PR interval greater than 200 milliseconds.					
Cardiac arrest	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by cessation of the pumping function of the heart.					
Chest pain - cardiac	Mild pain	Moderate pain; limiting instrumental ADL	Pain at rest; limiting self care ADL	-	-
Definition: A disorder characterized by substernal discomfort due to insufficient myocardial oxygenation.					
Conduction disorder	Mild symptoms; intervention not indicated	Moderate symptoms	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized 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 characterized by a thickened and fibrotic pericardial sac; these fibrotic changes impede normal myocardial function by restricting myocardial muscle 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 support)	Death
Definition: A disorder characterized by the inability of the heart to pump blood at an adequate volume to meet tissue metabolic requirements, or, the ability to do so only at an elevation in the filling pressure.					

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
Definition: A disorder characterized by failure of the left ventricle to produce adequate output despite an increase in distending pressure and in end-diastolic volume. Clinical manifestations mayinclude dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.					
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 characterized by a defect in mitral valve function 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
Definition: A disorder characterized by a dysrhythmia with relatively constant PR interval prior to the block of an atrial impulse. This is the result of intermittent failure of atrial electrical impulse conduction through the atrioventricular (AV) node to the ventricles.					
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
Definition: A disorder characterized by a dysrhythmia with a progressively lengthening PR interval prior to the blocking of an atrial impulse. This is the result of intermittent failure of atrial electrical impulse conduction through the atrioventricular (AV) node to the ventricles.					
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 characterized by gross necrosis of the myocardium; this is due to an interruption 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 characterized by inflammation of the muscle tissue of the heart.					
Palpitations	Mild symptoms; intervention not indicated	Intervention indicated	-	-	-
Definition: A disorder characterized by an unpleasant sensation of irregular and/or forceful beating of 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 characterized by a dysrhythmia with abrupt onset and sudden termination of atrial contractions with a rate of 150-250 beats per minute. The rhythm disturbance originates in the atria.					
Pericardial effusion	-	Asymptomatic effusion size small to moderate	Effusion with physiologic consequences	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by fluid collection within the pericardial sac, usually due to inflammation.					
Pericardial tamponade	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in intrapericardial pressure due to the collection of blood or fluid in the pericardium.					
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
Definition: A disorder characterized by irritation to the layers of the pericardium (the protective sac around the heart).					

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 characterized by a defect in pulmonary valve function or structure.					
Restrictive cardiomyopathy	-	-	Symptomatic heart failure or other cardiac symptoms, responsive to intervention	Refractory heart failure or other poorly controlled cardiac symptoms	Death
Definition: A disorder characterized by an inability of the ventricles to fill with blood because the myocardium (heart muscle) stiffens and loses its flexibility.					
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 characterized by impairment of right ventricular function associated with low ejection fraction and a decrease in motility 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
Definition: A disorder characterized by a dysrhythmia with alternating periods of bradycardia and atrial tachycardia accompanied by syncope, fatigue and dizziness.					
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 characterized by a dysrhythmia with a heart rate 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 characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates in the sinus node.					
Supraventricular tachycardia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates above the ventricles.					
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 characterized by a defect in tricuspid valve function 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 characterized by a dysrhythmia that originates in the ventricles.					
Ventricular fibrillation	-	-	-	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia without discernible QRS complexes due to rapid repetitive excitation of myocardial fibers without coordinated contraction of the ventricles.					
Ventricular tachycardia	-	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates distal to the bundle 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 characterized by the presence of an accessory conductive pathway between the atria and the ventricles that causes premature ventricular activation.					
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 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 characterized by a sensation of marked discomfort 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 characterized by inflammation, swelling and redness to the outer ear and ear canal.					
External ear 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 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 aids; threshold shift >20 dB at 3 kHz and above in at least one ear; additional speech-language related services indicated.	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.	-
Definition: A disorder characterized by partial or complete loss of the ability to detect or understand sounds resulting from damage to ear structures.					
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
Definition: A disorder characterized by inflammation (physiologic response to irritation), swelling and redness to the middle ear.					
Tinnitus	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by noise in the ears, such as ringing, buzzing, roaring or clicking.					
Vertigo	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation as if the external world were revolving around the patient (objective vertigo) or as if he himself were revolving in space (subjective vertigo).					
Vestibular disorder	-	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dizziness, imbalance, nausea, 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	Moderate symptoms; medical intervention indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder that occurs when the adrenal cortex does not produce enough of the hormone cortisol and in some cases, the hormone aldosterone. It may be due to a disorder of the adrenal cortex as in Addison's disease or primary adrenal insufficiency.					
Cushingoid	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms, medical intervention or hospitalization indicated	-	-
Definition: A disorder characterized by signs and symptoms that resemble Cushing's disease or syndrome: buffalo hump obesity, striations, adiposity, hypertension, diabetes, and osteoporosis, usually due to exogenous corticosteroids.					
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 characterized by unusually late sexual maturity.					
Growth accelerated	-	>= +2 SD (standard deviation) above mid parental height or target height	-	-	-
Definition: A disorder characterized by greater growth than expected for age.					
Hyperparathyroidism	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by an increase in production of parathyroid hormone by the parathyroid glands. This results in hypercalcemia (abnormally high levels of calcium in the blood).					
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 characterized by excessive levels of thyroid hormone in the body. Common causes include an overactive thyroid gland or thyroid hormone overdose.					
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 characterized by a decrease in production of parathyroid hormone by the parathyroid 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 characterized by a decrease in production of thyroid hormone by the thyroid gland.					
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 characterized by unusually early development of secondary sexual features; the onset of sexual maturation begins usually before age 8 for girls and before age 9 for boys.					
Virilization	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by inappropriate masculinization occurring in a female or prepubertal 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 disorders					
	Grade				
Adverse Event	1	2	3	4	5
Blurred vision	Intervention not indicated	Symptomatic; limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by visual perception of unclear or fuzzy images.					
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., cataract surgery)	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by partial or complete opacity of the crystalline lens of one or both eyes. This results in a decrease in visual acuity and eventual blindness if untreated.					
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 characterized by inflammation, swelling and redness to the conjunctiva of the eye.					
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 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	Symptomatic; multiple agents indicated; limiting instrumental ADL	Decrease in visual acuity (<20/40); limiting self care ADL	-	-
Definition: A disorder characterized 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 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 characterized by a sensation of marked discomfort in the eye.					
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 characterized by impaired eyelid function.					
Flashing lights	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by a sudden or brief burst of light.					
Floaters	Symptomatic but not limiting ADL	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.					
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 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	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 characterized by inflammation to the cornea of the eye.					
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 characterized by an inability to see clearly in dim light.					

Eye disorders					
	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	-
Definition: A disorder characterized by involvement of the optic nerve (second cranial nerve).					
Papilledema	Asymptomatic; no visual field defects	Symptomatic decline in 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 characterized by swelling around the optic disc.					
Photophobia	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by fear and avoidance of 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 characterized by the separation of the inner retina layers from the underlying 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 characterized by a small laceration of the retina, this occurs when the vitreous separates from the retina. Symptoms include flashes and floaters.					
Retinal vascular disorder	-	Topical medication indicated	Intravitreal medication; operative intervention indicated	-	-
Definition: A disorder characterized by pathological retinal blood vessels that adversely affects 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 involving 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 characterized by involvement of the sclera of the eye.					
Uveitis	Asymptomatic; clinical or diagnostic observations only	Anterior uveitis; medical intervention indicated	Posterior or pan-uveitis	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by inflammation to the uvea of the eye.					
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 characterized by blood extravasation into the vitreous humor.					
Watering eyes	Intervention not indicated	Intervention indicated	Operative intervention indicated	-	-
Definition: A disorder of excessive tearing in the eyes; it can be caused by overproduction 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 disorders					
	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 characterized by swelling of the abdomen.					
Abdominal 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 abdominal region.					
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 characterized 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 characterized by bleeding from the anal region.					
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 characterized 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
Definition: A disorder characterized by a necrotic process occurring in the anal region.					
Anal 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 anal region.					
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 characterized 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 characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the anal canal.					
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 characterized by accumulation of serous or hemorrhagic 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 characterized by subject-reported feeling of uncomfortable fullness of the abdomen.					
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 characterized 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	-	-
Definition: A disorder characterized by inflammation of the lip.					

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
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 characterized 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 characterized 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 characterized by bleeding from the colon.					
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
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents in the colon.					
Colonic perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the colonic wall.					
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 characterized 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 characterized by a circumscribed, inflammatory 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 characterized by irregular and infrequent or difficult 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 characterized by the decay of a tooth, in which 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 characterized by frequent and watery bowel movements.					
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	-	-
Definition: A disorder characterized by reduced salivary flow in the oral cavity.					

Gastrointestinal disorders					
	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 characterized by an abnormal communication between the duodenum and another 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 characterized by bleeding from the duodenum.					
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 characterized 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 characterized by a rupture in the duodenal wall.					
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 characterized 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 characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the duodenal wall.					
Dyspepsia	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; surgical intervention indicated	-	-
Definition: A disorder characterized by an uncomfortable, often painful feeling in the stomach, resulting from impaired digestion. Symptoms include burning stomach, bloating, heartburn, nausea and vomiting.					
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 characterized by difficulty in swallowing.					
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 characterized by inflammation of the small and 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 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	Life-threatening consequences; urgent intervention indicated	Death
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 or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the esophagus.					

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 characterized by a necrotic process occurring 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 characterized by blockage of the normal flow of the contents in the esophagus.					
Esophageal 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 esophageal region.					
Esophageal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the wall of the esophagus.					
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 characterized 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 characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the esophageal 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 characterized by bleeding from esophageal varices.					
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 characterized by inflammation of the esophageal wall.					
Fecal incontinence	Occasional use of pads required	Daily use of pads required	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by inability to control the escape of stool from the rectum.					
Flatulence	Mild symptoms; intervention not indicated	Moderate; persistent; psychosocial sequelae	-	-	-
Definition: A disorder characterized by a state of excessive gas in the alimentary canal.					
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 characterized by an abnormal communication between the stomach and another organ or anatomic site.					
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 characterized by bleeding from the gastric wall.					
Gastric 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 characterized by a necrotic process occurring in the gastric wall.					

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Gastric perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the stomach wall.					
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 characterized 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
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the stomach.					
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 characterized by inflammation of the stomach.					
Gastroesophageal reflux disease	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; surgical intervention indicated	-	-
Definition: A disorder characterized by reflux of the gastric and/or duodenal contents into the distal esophagus. It is chronic in nature and usually caused by incompetence of the lower esophageal sphincter, and may result in injury to the esophageal mucosal. Symptoms include heartburn and acid indigestion.					
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 characterized by an abnormal communication between any part of the gastrointestinal 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 characterized by a sensation of marked discomfort in the gastrointestinal region.					
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 characterized by an incomplete paralysis of the muscles of the stomach wall resulting in delayed emptying of the gastric contents into the small intestine.					
Gingival pain	Mild pain	Moderate pain interfering with oral intake	Severe pain; inability to aliment orally	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the gingival region.					
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 characterized by bleeding from the hemorrhoids.					
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 characterized by the presence of dilated veins in the rectum and surrounding area.					
Ileal 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 characterized by an abnormal communication between the ileum and another organ or anatomic site.					
Ileal 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 characterized by bleeding from the ileal wall.					

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Ileal 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 characterized by blockage of the normal flow of the intestinal contents in the ileum.					
Ileal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the ileal wall.					
Ileal 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 characterized by a narrowing of the lumen of the ileum.					
Ileal 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 characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the ileum.					
Ileus	-	Symptomatic; altered GI function; bowel rest indicated	Severely altered GI function; TPN indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by failure of the ileum to transport intestinal contents.					
Intra-abdominal hemorrhage	-	Medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding in the abdominal cavity.					
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 characterized by an abnormal communication between the jejunum and another 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 characterized by bleeding from the jejunal wall.					
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 characterized by blockage of the normal flow of the intestinal contents in the jejunum.					
Jejunal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized 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 characterized 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 characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the jejunum.					
Lip pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort of the lip.					

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Lower 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 characterized by bleeding from the lower gastrointestinal 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 characterized by inadequate absorption of nutrients in the small intestine. Symptoms include abdominal marked 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 characterized by inflammation of the oral mucosal.					
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 characterized by a queasy sensation and/or the urge to vomit.					
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 characterized by blockage of the normal flow of the contents in the stomach.					
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 characterized by an abnormal communication between the oral cavity and another 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 characterized by a burning or tingling sensation on the lips, tongue or entire mouth.					
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 characterized by bleeding from the mouth.					
Oral 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 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 characterized 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 characterized by an abnormal communication between the pancreas and another organ or anatomic site.					
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 characterized by bleeding from the pancreas.					
Pancreatic necrosis	-	-	Tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized 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
Definition: A disorder characterized by inflammation of the pancreas.					
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 gingival 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 characterized 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 characterized 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 characterized by an abnormal communication 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 characterized 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 characterized 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 characterized 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 characterized by blockage of the normal flow of the intestinal contents in the rectum.					
Rectal 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 rectal region.					
Rectal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized 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 characterized 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
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the rectum.					

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
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 characterized by bleeding from the retroperitoneal area.					
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 characterized 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 characterized by an abnormal communication between a salivary gland and another 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 characterized 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 characterized 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 characterized by a rupture in the small intestine 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 characterized 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 characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the small intestine.					
Stomach 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 stomach.					
Tooth development disorder	Asymptomatic; hypoplasia of tooth or enamel	Impairment correctable with oral surgery	Maldevelopment with impairment not surgically correctable; disabling	-	-
Definition: A disorder characterized by a pathological process of the teeth occurring during tooth development.					
Tooth discoloration	Surface stains	-	-	-	-
Definition: A disorder characterized by a change in tooth hue or tint.					
Toothache	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 tooth.					

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 characterized 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 characterized by bleeding from the upper gastrointestinal tract (oral cavity, pharynx, 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 characterized by the reflexive act of ejecting the contents of the stomach through 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

General disorders and administration site conditions					
	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 characterized by a sensation of cold that often marks a physiologic response to sweating after a fever.					
Death neonatal	-	-	-	-	Death
Definition: A disorder characterized by cessation of life occurring during 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 characterized by swelling due to excessive fluid 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 characterized by swelling due to excessive fluid accumulation in the upper or lower 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 characterized by swelling due to excessive fluid accumulation in the trunk area.					
Facial 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 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 characterized by a state of generalized weakness with a pronounced inability to summon sufficient energy to accomplish 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 characterized by elevation of the body's temperature above the upper limit of normal.					
Flu like symptoms	Mild flu-like symptoms present	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by a group of symptoms similar to those observed in patients with the flu. It includes fever, chills, body aches, malaise, loss of appetite and dry cough.					
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 characterized by walking difficulties.					
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
Definition: A disorder characterized by an abnormally low body temperature. Treatment is required when the body temperature is 35C (95F) or below.					

General disorders and administration site conditions					
	Grade				
Adverse 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 (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	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.					
Infusion site extravasation	-	Erythema with associated symptoms (e.g., edema, pain, induration, phlebitis)	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by leakage of a pharmacologic or a biologic substance from the infusion site into the surrounding tissue. Signs and symptoms include induration, erythema, swelling, burning sensation and marked discomfort at the infusion site.					
Injection site reaction	Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)	Pain; lipodystrophy; edema; phlebitis	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an intense adverse reaction (usually immunologic) developing at the site of an injection.					
Irritability	Mild; easily consolable	Moderate; limiting instrumental ADL; increased attention indicated	Severe abnormal or excessive response; limiting self care ADL; inconsolable	-	-
Definition: A disorder characterized by an abnormal responsiveness to stimuli or physiological arousal; may be in response to pain, fright, a drug, an emotional situation or a medical condition.					
Localized edema	Localized to dependent areas, no disability or functional impairment	Moderate localized edema and intervention indicated; limiting instrumental ADL	Severe localized edema and intervention indicated; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to excessive fluid accumulation at a specific anatomic site.					
Malaise	Uneasiness or lack of well being	Uneasiness or lack of well being; limiting instrumental ADL	-	-	-
Definition: A disorder characterized by a feeling of general discomfort or uneasiness, an out-of-sorts feeling.					
Multi-organ failure	-	-	Shock with azotemia and acid-base disturbances; significant coagulation abnormalities	Life-threatening consequences (e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic acidosis)	Death
Definition: A disorder characterized by progressive deterioration of the lungs, liver, kidney and clotting mechanisms.					
Neck edema	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	-	-
Definition: A disorder characterized by swelling due to an accumulation of excessive fluid in the neck.					
Non-cardiac chest pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by discomfort in the chest unrelated to a heart disorder.					
Pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by the sensation of marked discomfort, distress or agony.					
Sudden death NOS	-	-	-	-	Death
Definition: An unexpected cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.					
General disorders and administration site conditions - 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

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 characterized by a narrowing of the lumen of the bile duct.					
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 characterized by an abnormal communication between the bile ducts and another 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 characterized by inflammation involving the gallbladder. It may be associated with 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 characterized by an abnormal communication between the gallbladder and another organ or anatomic site.					
Gallbladder necrosis	-	-	-	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring 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
Definition: A disorder characterized by blockage of the normal flow of the contents of the gallbladder.					
Gallbladder 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 gallbladder region.					
Gallbladder perforation	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the gallbladder wall.					
Hepatic failure	-	-	Asterixis; mild encephalopathy; limiting self care ADL	Moderate to severe encephalopathy; coma; life-threatening consequences	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, lactic dehydrogenase, and alkaline phosphatase.					
Hepatic hemorrhage	Mild; intervention not indicated	Symptomatic; medical intervention indicated	Transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the liver.					
Hepatic necrosis	-	-	-	Life-threatening consequences; urgent radiologic or operative intervention 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 indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the wall of the extrahepatic or intrahepatic bile duct.					

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 characterized by an increase in blood pressure in the portal venous system.					
Portal vein thrombosis	-	Intervention not indicated	Medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized 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; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Immune system disorders					
	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
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.					
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and 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 from loss of function or tissue destruction of an organ or multiple organs, arising from humoral or cellular immune responses of the individual to his own tissue constituents.					
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 characterized by nausea, headache, tachycardia, hypotension, rash, and shortness 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
Definition: A disorder characterized by a delayed-type hypersensitivity reaction to foreign proteins derived from an animal serum. It occurs approximately six to twenty-one days following the administration of the foreign antigen. Symptoms include fever, arthralgias, myalgias, skin eruptions, lymphadenopathy, chest marked discomfort and dyspnea.					
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 infestations					
	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 characterized by an infectious process involving 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
Definition: A disorder characterized by an infectious process involving the anal area and the rectum.					
Appendicitis	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by acute inflammation to the vermiform appendix caused by a pathogenic agent.					
Appendicitis perforated	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by acute inflammation to the vermiform appendix caused by a pathogenic agent with gangrenous changes resulting in the rupture of the appendiceal wall. The appendiceal wall rupture causes the release of inflammatory and bacterial contents from the appendiceal lumen into the abdominal cavity.					
Arteritis infective	-	-	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 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 characterized by an infectious process involving 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 characterized by an infectious process involving 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 characterized by an infectious process involving the bones.					
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
Definition: A disorder characterized by an infectious process involving the breast.					
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 characterized by an infectious process involving 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 characterized 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 infestations					
	Grade				
Adverse Event	1	2	3	4	5
Definition: A disorder characterized by an infectious process involving 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
Definition: A disorder characterized by an infectious process involving the uterine cervix.					
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 characterized by an infectious process involving the conjunctiva. Clinical manifestations 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 characterized by an infectious process involving 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 characterized by an infectious process involving 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
Definition: A disorder characterized by an infectious process involving the use of a medical device.					
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 characterized by an infectious process involving 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 characterized by an infectious process involving the brain tissue.					
Encephalomyelitis infection	-	-	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 brain and spinal cord tissues.					
Endocarditis infective	-	-	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 endocardial layer of the heart.					
Endophthalmitis	-	Local intervention indicated	Systemic intervention or hospitalization indicated	Blindness (20/200 or worse)	-
Definition: A disorder characterized by an infectious process involving the internal structures of the eye.					

Infections and infestations					
	Grade				
Adverse Event	1	2	3	4	5
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: A disorder characterized by an infectious process involving the small and large intestines.					
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 characterized by an infectious process involving 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 characterized by an infectious process involving 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 characterized by an infectious process involving 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 characterized by an infectious process involving 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 characterized by an infectious process involving the liver.					
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 characterized by a viral pathologic process involving 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 characterized by an infectious process involving 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 characterized by an infectious process involving a joint.					
Kidney infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the kidney.					

Infections and infestations					
	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 characterized 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 characterized by an infectious process involving 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 characterized by an infectious process involving 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 characterized by an infectious process involving the lymph nodes.					
Mediastinal infection	-	-	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 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 characterized 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 characterized by an infectious process involving 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 characterized by an infectious process involving 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
Definition: A disorder characterized by an infectious process involving the outer ear and ear canal. Contributory factors include excessive water exposure (swimmer's ear infection) and cuts in the ear canal. Symptoms include fullness, itching, swelling and marked discomfort in the ear and ear drainage.					
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 characterized by an infectious process involving 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 intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the ovary.					

Infections and infestations					
	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 characterized by an infectious process involving 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; life-threatening consequences	Death
Definition: A disorder characterized by an eruption consisting of papules (a small, raised pimple) and pustules (a small pus filled blister), typically appearing in face, scalp, and upper chest and back Unlike acne, this rash does not present with whiteheads or blackheads, and can be symptomatic, with itchy or tender lesions.					
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 characterized by an infectious process involving the soft tissues around the nail.					
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 characterized by an infectious process involving the pelvic cavity.					
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 characterized by an infectious process involving 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
Definition: A disorder characterized by an infectious process involving the orbit of the eye.					
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
Definition: A disorder characterized by an infectious process involving the peripheral nerves.					
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 characterized by an infectious process involving the peritoneum.					
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 characterized 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 characterized by an infectious process involving the vein. Clinical manifestations include erythema, marked discomfort, swelling, and induration along the course of the infected vein.					
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 characterized by an infectious process involving 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 characterized by an infectious process involving 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 characterized by a circumscribed and elevated skin lesion filled with pus.					
Rhinitis 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	-	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 characterized by an infectious process involving 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 characterized by an infectious process involving the scrotum.					
Sepsis	-	-	-	Life-threatening consequences; urgent intervention indicated	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 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 characterized by an infectious process involving 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
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	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the small intestine.					
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 characterized by an infectious process involving soft tissues.					
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				
Adverse Event	1	2	3	4	5
Definition: A disorder characterized by an infectious process involving the spleen.					
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 characterized by an infectious process involving a stoma (surgically created opening 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 characterized by an infectious process involving 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 characterized by an infectious process involving the trachea.					
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 characterized by an infectious process involving the upper respiratory tract (nose, paranasal sinuses, pharynx, larynx, 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 characterized by an infectious process involving 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 characterized by an infectious process involving the urinary tract, most commonly 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 characterized by an infectious process involving the endometrium. It may extend to the myometrium and parametrial 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 characterized by an infectious process involving 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 characterized by an infectious process involving 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 characterized by an infectious process involving the wound.					
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 indicated	Limiting instrumental ADL; operative intervention indicated	Limiting self care ADL; elective surgery indicated	-	-
Definition: A finding of damage to the ankle joint characterized by a break in the continuity of the ankle bone. Symptoms include marked discomfort, swelling and difficulty moving the affected leg and foot.					
Aortic injury	-	-	Severe symptoms; limiting self care ADL; disabling; repair or revision indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to the aorta.					
Arterial injury	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); repair or revision not indicated	Severe symptoms; limiting self care ADL; disabling; repair or revision indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to an artery.					
Biliary 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 bile due to breakdown of a biliary anastomosis (surgical connection of two separate anatomic structures).					
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 of urine due to breakdown of a bladder anastomosis (surgical connection of two separate anatomic structures).					
Bruising	Localized or in a dependent area	Generalized	-	-	-
Definition: A finding of injury of the soft tissues or bone characterized by leakage of blood into surrounding tissues.					
Burn	Minimal symptoms; intervention not indicated	Medical intervention; minimal debridement indicated	Moderate to major debridement or reconstruction indicated	Life-threatening consequences	Death
Definition: A finding of impaired integrity to the anatomic site of an adverse thermal reaction. Burns can be caused by exposure to chemicals, direct heat, electricity, flames and radiation. The extent of damage depends on the length and intensity of exposure and time until provision of treatment.					
Dermatitis radiation	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 cutaneous inflammatory reaction occurring as a result of exposure to biologically effective levels of ionizing radiation.					
Esophageal 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 due to breakdown of an esophageal anastomosis (surgical connection of two separate anatomic structures).					
Fall	Minor with no resultant injuries; intervention not indicated	Symptomatic; noninvasive intervention indicated	Hospitalization indicated	-	-
Definition: A finding of sudden movement downward, usually resulting in injury.					
Fallopian tube anastomotic leak	Asymptomatic; clinical or 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 due to breakdown of a fallopian tube anastomosis (surgical connection of two separate anatomic structures).					
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 diagnostic observations only; intervention not indicated	Symptomatic but non-displaced; immobilization indicated	Severe symptoms; displaced or open wound with bone exposure; disabling; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of traumatic injury to the bone in which the continuity of the bone is broken.					

Injury, poisoning and procedural complications					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Gastric 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 due to breakdown of a gastric anastomosis (surgical connection of two separate anatomic structures).					
Gastrointestinal 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 due to breakdown of a gastrointestinal anastomosis (surgical connection of two separate anatomic structures).					
Gastrointestinal stoma necrosis	-	Superficial necrosis; intervention not indicated	Severe symptoms; hospitalization or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of a necrotic process occurring in the gastrointestinal tract stoma.					
Hip fracture	-	Hairline fracture; mild pain; limiting instrumental ADL; non-surgical intervention indicated	Severe pain; hospitalization or intervention indicated for pain control (e.g., traction); operative intervention indicated	Life-threatening consequences; symptoms associated with neurovascular compromise	-
Definition: A finding of traumatic injury to the hip in which the continuity of either the femoral head, femoral neck, intertrochanteric or subtrochanteric regions is broken.					
Injury to carotid artery	-	-	Severe symptoms; limiting self care ADL (e.g., transient cerebral ischemia); repair or revision indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the carotid artery.					
Injury to inferior vena cava	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the inferior vena cava.					
Injury to jugular vein	-	-	Symptomatic limiting self care ADL; disabling; repair or revision indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the jugular vein.					
Injury to superior vena cava	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; repair or revision not indicated	Severe symptoms; limiting self care ADL; disabling; repair or revision indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to the superior vena cava.					
Intestinal stoma 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 contents from an intestinal stoma (surgically created opening on the surface of the body).					
Intestinal stoma obstruction	-	Self-limited; intervention not indicated	Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of blockage of the normal flow of the contents of the intestinal stoma.					
Intestinal stoma 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 leakage from the intestinal stoma.					
Intraoperative arterial 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 an artery during a surgical procedure.					
Intraoperative breast 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

Injury, poisoning and procedural complications					
	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
Definition: A finding of damage to the heart during a surgical procedure.					
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
Definition: A finding of damage to the ear during a surgical procedure.					
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 surgical 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 during 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 surgical procedure.					
Intraoperative hemorrhage	-	-	Postoperative radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of uncontrolled bleeding during a surgical procedure.					
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 biliary tract during a surgical procedure.					
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 the musculoskeletal system during a surgical procedure.					
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
Definition: A finding of damage to the nervous system during a surgical procedure.					
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 procedure.					
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 procedure.					
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; disabling	Life-threatening consequences; urgent intervention indicated	Death

Injury, poisoning and procedural complications					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A finding of damage to the reproductive organs during a surgical procedure.					
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 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 procedure.					
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 the spleen during a surgical procedure.					
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 the urinary system during a surgical procedure.					
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 a vein during a surgical procedure.					
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 kidney anastomosis (surgical connection of two separate anatomic structures).					
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 due to breakdown of an anastomosis (surgical connection of two separate anatomic structures) in the large 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 due to breakdown of a pancreatic anastomosis (surgical connection of two separate anatomic structures).					
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 due to breakdown of a pharyngeal anastomosis (surgical connection of two separate anatomic structures).					
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 occurring after a surgical procedure.					
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 previously undocumented problem that occurs after a thoracic procedure.					
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 surface.					
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 displacement 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 chemotherapeutic agents, for weeks or months following radiotherapy. The inflammatory reaction is confined to the previously irradiated skin and the symptoms disappear after the removal of the pharmaceutical agent.					
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 due to breakdown of a rectal anastomosis (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.					
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 due to breakdown of an anastomosis (surgical connection of two separate anatomic structures) in the small 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 due to breakdown of a spermatic cord anastomosis (surgical connection of two separate anatomic structures).					
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 continuity of a vertebral bone is broken.					
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 (surgically created opening on the surface of the body).					
Stomal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the jejunal mucosal surface close to the anastomosis site following a gastroenterostomy procedure.					
Tracheal hemorrhage	Minimal bleeding identified on clinical or diagnostic 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 trachea.					
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
Definition: A finding of blockage of the lumen of the trachea.					

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 leakage 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
Definition: A finding of leakage due to breakdown of a ureteral anastomosis (surgical connection of two separate anatomic structures).					
Urethral 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 due to breakdown of a urethral anastomosis (surgical connection of two 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 contents from a urostomy.					
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 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 due to breakdown of a uterine anastomosis (surgical connection of two 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
Definition: A disorder characterized by a rupture in the uterine wall.					
Vaginal 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 due to breakdown of a vaginal anastomosis (surgical connection of two separate anatomic structures).					
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 due to breakdown of a vas deferens anastomosis (surgical connection of two separate anatomic structures).					
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
Definition: A finding of a previously undocumented problem related to the vascular access site.					

Injury, poisoning and procedural 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
Definition: A finding of development of a new problem at the site of an existing wound.					
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 dehiscence 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.					
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 broken.					
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	-	-
Definition: An abnormal laboratory test result in which the partial thromboplastin time is found to be greater than the control value. As a possible indicator of coagulopathy, a prolonged partial thromboplastin time (PTT) may occur in a variety of diseases and disorders, both primary and related to treatment.					
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 laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in 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 laboratory test results that indicate an increase in the level of alkaline phosphatase 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 laboratory test results that indicate an 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 laboratory test results that indicate abnormal levels of antidiuretic hormone 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 laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated 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 laboratory test results that indicate an decrease in levels of corticotrophin 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 laboratory test results that indicate abnormal levels of gonadotrophin hormone 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 laboratory test results that indicate abnormal levels of prolactin hormone 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 lung 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 which indicates increased levels of cardiac troponin I in a biological specimen.					
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 biological specimen.					
CD4 lymphocytes decreased	<LLN - 500/mm3; <LLN - 0.5 x 10e9 /L	<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 laboratory test results that indicate an decrease in levels of CD4 lymphocytes 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 laboratory test results that indicate higher than normal levels of cholesterol 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 laboratory test results that indicate an increase in levels of creatine phosphokinase 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 laboratory test results that indicate increased levels of creatinine in a biological 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 computed when the amount of blood ejected during a ventricular contraction of the heart is compared to the amount that was present prior to the contraction.					
Electrocardiogram QT corrected interval prolonged	QTc 450 - 480 ms	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 dysrhythmia characterized by an abnormally long corrected QT interval.					
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 laboratory test results that indicate an decrease in levels of fibrinogen 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 test results that indicate a relative decrease 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 laboratory test results that indicate higher than normal levels of the enzyme gamma-glutamyltransferase in the blood specimen. GGT (gamma-glutamyltransferase) catalyzes the transfer of a gamma glutamyl group from a gamma glutamyl peptide to another peptide, amino acids 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 laboratory test results that indicate abnormal levels of growth hormone in a biological specimen.					
Haptoglobin decreased	<LLN	-	-	-	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of haptoglobin 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 laboratory test results that indicate increased 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 laboratory test results that indicate an increase in the ratio of the patient's prothrombin time to a control sample 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 laboratory test results that indicate an increase in the level of lipase in a biological specimen.					
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9 /L	<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 laboratory test results that indicate a decrease in number of lymphocytes in a blood specimen.					
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	-
Definition: A finding based on laboratory test results that indicate an abnormal increase in the number of lymphocytes in the blood, effusions or bone marrow.					
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<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 laboratory test results that indicate a decrease in number of neutrophils in a blood specimen.					
Pancreatic enzymes decreased	<LLN and asymptomatic	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency	-	-
Definition: A finding based on laboratory test results that indicate an 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/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-
Definition: A finding based on laboratory 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 laboratory test results that indicate an 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 test results that indicate urine production is less relative to previous output.					
Vital capacity abnormal	90 - 75% of predicted value	<75 - 50% of predicted value; limiting instrumental ADL	<50% of predicted value; limiting self care ADL	-	-
Definition: A finding based on pulmonary function test results that indicate an abnormal vital capacity (amount of exhaled after a maximum inhalation) when compared to the predicted value.					
Weight gain	5 - <10% from baseline	10 - <20% from baseline	>=20% from baseline	-	-
Definition: A finding characterized by an increase in overall body weight; for pediatrics, greater than the baseline growth curve.					
Weight loss	5 to <10% from baseline; intervention not indicated	10 - <20% from baseline; nutritional support indicated	>=20% from baseline; tube feeding or TPN indicated	-	-
Definition: A finding characterized by a decrease in overall body weight; for pediatrics, less than the baseline growth curve.					
White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate an decrease in number of white blood cells in a blood specimen.					
Investigations - 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

Metabolism and nutrition disorders					
	Grade				
Adverse Event	1	2	3	4	5
Acidosis	pH <normal, but >=7.3	-	pH <7.3	Life-threatening consequences	Death
Definition: A disorder characterized by abnormally high acidity (high hydrogen-ion concentration) of the blood and other body tissues.					
Alcohol intolerance	-	Present	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in sensitivity to the adverse effects of alcohol, which can include nasal congestion, skin flushes, heart dysrhythmias, nausea, vomiting, indigestion and headaches.					
Alkalosis	pH >normal, but <=7.5	-	pH >7.5	Life-threatening consequences	Death
Definition: A disorder characterized by abnormally high alkalinity (low hydrogen-ion concentration) of the blood and other body tissues.					
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 characterized 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 characterized by excessive loss of water from the body. It is usually caused by severe diarrhea, vomiting or diaphoresis.					
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 characterized by an inability to properly metabolize 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; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of calcium (corrected for albumin) 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 characterized by laboratory test results that indicate an elevation in the concentration of blood sugar. It is usually an indication of diabetes mellitus or glucose intolerance.					
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 characterized by laboratory test results that indicate an elevation in the concentration of potassium in the blood; associated with kidney failure or sometimes with the use of diuretic drugs.					
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 characterized by laboratory test results that indicate an elevation in the concentration of magnesium in the blood.					
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of sodium in the blood.					
Hypertriglyceridemia	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
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of triglyceride concentration in the blood.					
Hyperuricemia	>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
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of uric acid.					
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of albumin in the blood.					

Metabolism and nutrition disorders					
	Grade				
Adverse Event	1	2	3	4	5
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized 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 characterized by laboratory test results that indicate a low concentration of calcium (corrected for albumin) in the blood.					
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<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 characterized by laboratory test results that indicate a low concentration of glucose in the blood.					
Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of potassium in the blood.					
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<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 characterized by laboratory test results that indicate a low concentration of magnesium in the blood.					
Hyponatremia	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of sodium in the blood.					
Hypophosphatemia	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<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 characterized by laboratory test results that indicate a low concentration of phosphates in the blood.					
Iron overload	-	Moderate symptoms; intervention not indicated	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by accumulation of iron in the tissues.					
Obesity	-	BMI 25 - 29.9 kg/m2	BMI 30 - 39.9 kg/m2	BMI >=40 kg/m2	-
Definition: A disorder characterized by having a high amount of body fat.					
Tumor lysis syndrome	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by metabolic abnormalities that result from a spontaneous or therapy-related cytolysis of tumor cells.					
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				
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 characterized by a necrotic process occurring in the soft tissues of the abdominal wall.					
Arthralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in a joint.					
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 characterized by inflammation involving a joint.					
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
Definition: A disorder characterized by necrotic changes in the bone tissue due to interruption of blood supply. Most often affecting the epiphysis of the long bones, the necrotic changes result in the collapse and the destruction of the bone structure.					
Back pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the back region.					
Bone pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the bones.					
Buttock pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the buttocks.					
Chest wall pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation 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 characterized 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 characterized 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 characterized by marked discomfort sensation on the lateral side of the body in the region below the ribs and above 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 characterized by a reduction in the strength of muscles in multiple anatomic sites.					
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	-	-
Definition: A disorder characterized by of stature that is smaller than normal as expected for age.					

Musculoskeletal and connective tissue disorders					
	Grade				
Adverse Event	1	2	3	4	5
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 characterized 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 characterized by excessive fluid in a joint, usually as a result of joint inflammation.					
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 characterized 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 characterized by a decrease in flexibility of a cervical spine joint.					
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 characterized 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 characterized by an abnormal increase in the curvature of the thoracic portion 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 characterized 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 characterized by a reduction in the strength of the muscles on the left side of the 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 characterized by a reduction in the strength of 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 characterized by a reduction in the strength of the muscles on the right side of the body.					
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	-	-
Definition: A disorder characterized by a reduction in the strength of the trunk muscles.					
Muscle weakness upper 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 characterized by a reduction in the strength of the upper limb muscles.					

Musculoskeletal and connective tissue disorders					
	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 characterized by of a malformation of the musculoskeletal system.					
Myalgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation originating from a muscle or group 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 characterized by inflammation involving the skeletal muscles.					
Neck pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the neck area.					
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 characterized 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 characterized 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 characterized by reduced bone mass, with a decrease in cortical thickness and in the number and size of the trabeculae of cancellous bone (but normal chemical composition), resulting in increased fracture incidence.					
Pain in extremity	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the upper or lower extremities.					
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
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the pelvis.					
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 characterized by a malformed, lateral curvature 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 characterized by a necrotic process occurring in the soft tissues of the lower extremity.					
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
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the upper extremity.					

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 characterized 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 characterized by lack of ability to open the mouth 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	Severe length discrepancy >5 cm; limiting self care ADL; disabling; operative intervention indicated	-	-
Definition: A disorder characterized by of a discrepancy between the lengths of the lower or upper extremities.					
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 benign, malignant and unspecified (incl cysts and polyps)					
	Grade				
Adverse Event	1	2	3	4	5
Leukemia secondary to oncology chemotherapy	-	-	-	Present	Death
Definition: A disorder characterized by leukemia arising as a result of the mutagenic effect of chemotherapy agents.					
Myelodysplastic syndrome	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by insufficiently healthy hematapoietic cell production by the bone marrow.					
Treatment related secondary malignancy	-	-	Non life-threatening secondary malignancy	Acute life-threatening secondary malignancy; blast crisis in leukemia	Death
Definition: A disorder characterized by development of a malignancy most probably as a result of treatment for a previously existing malignancy.					
Tumor pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort from a neoplasm that may be pressing on a nerve, blocking blood vessels, inflamed or fractured from metastasis.					
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					
	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 characterized by involvement of the abducens nerve (sixth cranial nerve).					
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 characterized by involvement of the accessory 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 characterized by involvement of the acoustic nerve (eighth cranial nerve).					
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 characterized by an uncomfortable feeling of inner restlessness and inability to stay still; this is a side effect of some psychotropic drugs.					
Amnesia	Mild; transient memory loss	Moderate; short term memory loss; limiting instrumental ADL	Severe; long term memory loss; limiting self care ADL	-	-
Definition: A disorder characterized by systematic and extensive loss of memory.					
Aphonia	-	-	Voicelessness; unable to speak	-	-
Definition: A disorder characterized by the inability to speak. It may result from injuries to the vocal cords or may be functional (psychogenic).					
Arachnoiditis	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the arachnoid membrane and adjacent subarachnoid space.					
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 characterized by lack of coordination of muscle movements resulting in the impairment or inability to perform voluntary 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 characterized by regional paresthesia of the brachial plexus, marked discomfort and muscle weakness, and limited 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 characterized by a necrotic process occurring 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 characterized by loss of cerebrospinal fluid into 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 characterized by a conspicuous change in cognitive 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	-	-
Definition: A disorder characterized by a deterioration in the ability to concentrate.					

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 characterized by a decrease in ability to perceive and respond.					
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 characterized by a disturbing sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking.					
Dysarthria	Mild slurred speech	Moderate impairment of articulation or slurred speech	Severe impairment of articulation or slurred speech	-	-
Definition: A disorder characterized by slow and slurred speech resulting from an inability to coordinate 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 characterized by distortion of sensory perception, 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 characterized by abnormal sensual experience with the taste of foodstuffs; it can 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 characterized by impairment of verbal communication skills, often resulting from brain damage.					
Edema cerebral	-	-	-	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the brain.					
Encephalopathy	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a pathologic process involving the brain.					
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 characterized by abnormal, repetitive, involuntary muscle movements, frenzied speech and extreme restlessness.					
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 characterized by a reduction in the strength 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 characterized by involvement of the facial nerve (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 characterized by involvement of the glossopharyngeal nerve (ninth cranial nerve).					
Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in various parts of the head, not confined to the area of distribution 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 characterized by an abnormal increase of cerebrospinal fluid in the ventricles of the brain.					
Hypersomnia	Mild increased need for sleep	Moderate increased need for sleep	Severe increased need for sleep	-	-
Definition: A disorder characterized 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 diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the hypoglossal 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 characterized by bleeding from the cranium.					
Ischemia cerebrovascular	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	-	-	-
Definition: A disorder characterized by a decrease or absence of blood supply to the brain caused by obstruction (thrombosis or embolism) of an artery resulting in neurological damage.					
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 characterized by involvement of the trochlear nerve (fourth cranial nerve).					
Lethargy	Mild symptoms; reduced alertness and awareness	Moderate symptoms; limiting instrumental ADL	-	-	-
Definition: A disorder characterized by a decrease in consciousness characterized by mental and physical 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 characterized by diffuse reactive astrocytosis with multiple areas of necrotic foci without inflammation.					
Memory impairment	Mild memory impairment	Moderate memory impairment; limiting instrumental ADL	Severe memory impairment; limiting self care ADL	-	-
Definition: A disorder characterized by a deterioration in memory function.					
Meningismus	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by neck stiffness, headache, and photophobia resulting from irritation of the cerebral meninges.					
Movements involuntary	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by uncontrolled and purposeless movements.					
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 characterized by inflammation involving the spinal cord. Symptoms include weakness, paresthesia, sensory loss, marked discomfort and incontinence.					
Neuralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by intense painful sensation along a nerve or group of nerves.					
Nystagmus	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involuntary movements of the eyeballs.					
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 characterized by involvement of the oculomotor nerve (third cranial nerve).					
Olfactory nerve disorder	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the olfactory nerve (first cranial nerve).					

Nervous system disorders					
	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 characterized by functional disturbances of sensory neurons resulting in abnormal cutaneous sensations of tingling, numbness, pressure, cold, and warmth that are experienced in the absence of a stimulus.					
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 characterized by inflammation or degeneration 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 characterized by inflammation or degeneration of the peripheral sensory nerves.					
Phantom pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort related to a limb or an organ that is removed from or is not physically part of the body.					
Presyncope	-	Present (e.g., near fainting)	-	-	-
Definition: A disorder characterized by an episode of lightheadedness and dizziness which may precede an episode of syncope.					
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
Definition: A disorder characterized by dysfunction of the corticospinal (pyramidal) tracts of the spinal cord. Symptoms include an increase in the muscle tone in the lower extremities, hyperreflexia, positive Babinski and a decrease in fine motor coordination.					
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 characterized by inflammation involving a nerve root. Patients experience marked discomfort radiating along a nerve path because of spinal pressure on the connecting nerve root.					
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 characterized by paralysis of the recurrent laryngeal 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
Definition: A disorder characterized by headaches, mental status changes, visual disturbances, and seizures associated with imaging findings of posterior leukoencephalopathy. It has been observed in association with hypertensive encephalopathy, eclampsia, and immunosuppressive and cytotoxic drug treatment. It is an acute or subacute reversible condition.					
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 characterized by a sudden, involuntary skeletal muscular contractions of cerebral or brain stem origin.					
Sinus pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort in the face, between the eyes, or upper teeth 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 characterized 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 by increased involuntary muscle tone that affects the regions interfering with voluntary movement. It results in gait, movement, and speech disturbances.					
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 characterized by a sudden loss of sensory function due to an intracranial vascular event.					
Syncope	-	-	Fainting; orthostatic collapse	-	-
Definition: A disorder characterized by spontaneous loss of consciousness caused by insufficient blood supply to the brain.					

Nervous system disorders					
	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 characterized by a brief attack (less than 24 hours) of cerebral dysfunction of vascular origin, with no persistent neurological deficit.					
Tremor	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by the uncontrolled shaking movement of the whole body or individual 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 characterized by involvement of the trigeminal 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 characterized by involvement of the vagus nerve (tenth cranial nerve).					
Vasovagal reaction	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a sudden drop of the blood pressure, bradycardia, and peripheral vasodilation that may lead to loss of consciousness. It results from an increase in the stimulation of the vagus nerve.					
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

Pregnancy, puerperium and perinatal conditions					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Fetal death	-	-	-	-	Fetal loss at any gestational age
Definition: A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without 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 characterized by inhibition of fetal growth resulting 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 characterized by delivery of a viable infant before the normal end of gestation. Typically, viability is achievable between the twentieth and thirty-seventh week of gestation.					
Unintended pregnancy	-	-	Unintended pregnancy	-	-
Definition: A disorder characterized by an unexpected pregnancy at 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; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Psychiatric disorders					
	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
Definition: A disorder characterized by a state of restlessness associated with unpleasant feelings of irritability and tension.					
Anorgasmia	Inability to achieve orgasm not adversely affecting relationship	Inability to achieve orgasm adversely affecting relationship	-	-	-
Definition: A disorder characterized by an inability to achieve orgasm.					
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 characterized by apprehension of danger and dread accompanied by restlessness, tension, tachycardia, and dyspnea unattached to a clearly identifiable stimulus.					
Confusion	Mild disorientation	Moderate disorientation; limiting instrumental ADL	Severe disorientation; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a lack of clear and orderly thought and behavior.					
Delayed orgasm	Delay in achieving orgasm not adversely affecting relationship	Delay in achieving orgasm adversely affecting relationship	-	-	-
Definition: A disorder characterized by sexual dysfunction characterized by a delay in climax.					
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 characterized by the acute and sudden development of confusion, illusions, movement changes, inattentiveness, agitation, and hallucinations. Usually, it is a reversible condition.					
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 characterized by false personal beliefs held contrary to reality, despite contradictory evidence and common sense.					
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 characterized by melancholic feelings of grief or unhappiness.					
Euphoria	Mild mood elevation	Moderate mood elevation	Severe mood elevation (e.g., hypomania)	-	-
Definition: A disorder characterized by an exaggerated feeling of well-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 characterized by a false sensory perception in the absence of an external stimulus.					
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 characterized by difficulty in falling asleep and/or remaining asleep.					
Libido decreased	Decrease in sexual interest not adversely affecting relationship	Decrease in sexual interest adversely affecting relationship	-	-	-
Definition: A disorder characterized 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 characterized 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 characterized by excitement of psychotic proportions manifested by mental and physical hyperactivity, disorganization 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 disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A disorder characterized by a conspicuous change in a 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 characterized by personality change, impaired functioning, and loss of touch with reality. It may be a manifestation of schizophrenia, bipolar disorder or brain tumor.					
Restlessness	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by an inability to rest, relax or be 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 characterized by thoughts of taking one's own 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 characterized by self-inflicted harm in an attempt 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	Creatinine 2 - 3 x above baseline	Creatinine >3 x baseline or >4.0 mg/dL; hospitalization indicated	Life-threatening consequences; dialysis indicated	Death
Definition: A disorder characterized by the acute loss of renal function and is traditionally classified as pre-renal (low blood flow into kidney), renal (kidney damage) and post-renal causes (ureteral or bladder outflow obstruction).					
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 characterized by a rupture in the bladder wall.					
Bladder spasm	Intervention not indicated	Antispasmodics indicated	Hospitalization indicated	-	-
Definition: A disorder characterized by a sudden and involuntary contraction of the bladder wall.					
Chronic kidney disease	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN - 60 ml/min/1.73 m2 or proteinuria 2+ present; urine protein/creatinine >0.5	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 characterized by gradual and usually permanent loss of kidney function resulting 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 characterized by inflammation of the bladder which is not caused by an infection 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 characterized by laboratory test results that indicate blood in the urine.					
Hemoglobinuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characterized by laboratory test results that indicate the presence of free hemoglobin 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 characterized by laboratory test results that indicate the presence of excessive protein in the urine. It is predominantly 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 characterized by the formation of crystals in the 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	-	-
Definition: A disorder characterized by paroxysmal and severe flank marked discomfort radiating to the inguinal area. Often, the cause is the passage of kidney stones.					

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 characterized 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 characterized by an abnormal communication between any part of the urinary system and another organ or anatomic site.					
Urinary frequency	Present	Limiting instrumental ADL; medical management indicated	-	-	-
Definition: A disorder characterized by urination at short intervals.					
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 characterized by inability to control the flow of 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 characterized by accumulation of urine within the bladder because of the inability 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 characterized 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 characterized by a sensation of marked discomfort in the urinary tract.					
Urinary urgency	Present	Limiting instrumental ADL; medical management indicated	-	-	-
Definition: A disorder characterized by a sudden compelling urge to urinate.					
Urine discoloration	Present	-	-	-	-
Definition: A disorder characterized 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

Reproductive system and breast disorders					
	Grade				
Adverse Event	1	2	3	4	5
Azoospermia	-	-	Absence of sperm in ejaculate	-	-
Definition: A disorder characterized by laboratory test results that indicate complete absence of spermatozoa in the semen.					
Breast atrophy	Minimal asymmetry; minimal atrophy	Moderate asymmetry; moderate atrophy	Asymmetry >1/3 of breast volume; severe atrophy	-	-
Definition: A disorder characterized by underdevelopment of the breast.					
Breast pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the breast region.					
Dysmenorrhea	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by abnormally painful abdominal cramps during menses.					
Dyspareunia	Mild discomfort or pain associated with vaginal penetration; discomfort relieved with use of vaginal lubricants or estrogen	Moderate discomfort or pain associated with vaginal penetration; discomfort or pain partially relieved with use of vaginal lubricants or estrogen	Severe discomfort or pain associated with vaginal penetration; discomfort or pain unrelieved by vaginal lubricants or estrogen	-	-
Definition: A disorder characterized by painful or difficult coitus.					
Ejaculation disorder	Diminished ejaculation	Anejaculation or retrograde ejaculation	-	-	-
Definition: A disorder characterized by problems related to ejaculation. This category includes premature, delayed, retrograde and painful ejaculation.					
Erectile dysfunction	Decrease in erectile function (frequency or rigidity of erections) but intervention not indicated (e.g., medication or use of mechanical device, penile pump)	Decrease in erectile function (frequency/rigidity of erections), erectile intervention indicated, (e.g., medication or mechanical devices such as penile pump)	Decrease in erectile function (frequency/rigidity of erections) but erectile intervention not helpful (e.g., medication or mechanical devices such as penile pump); placement of a permanent penile prosthesis indicated (not previously present)	-	-
Definition: A disorder characterized by the persistent or recurrent inability to achieve or to maintain an erection during sexual activity.					
Fallopian tube obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by blockage of the normal flow of the contents in the fallopian tube.					
Fallopian tube stenosis	Asymptomatic clinical or 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 disorder characterized by a narrowing of the fallopian tube lumen.					
Female genital tract 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 characterized by an abnormal communication between a female reproductive system organ and another organ or anatomic site.					
Feminization acquired	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by the development of secondary female sex characteristics in males due to extrinsic factors.					
Genital edema	Mild 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	Lymphorrhea; gross deviation from normal anatomic contour; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the genitals.					
Gynecomastia	Asymptomatic breast enlargement	Symptomatic (e.g., pain or psychosocial impact)	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by excessive development of the breasts in males.					
Hematosalpinx	Minimal bleeding identified on imaging study or laparoscopy; 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

Reproductive system and breast disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A disorder characterized by the presence of blood in a fallopian tube.					
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 characterized by irregular cycle or duration of menses.					
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 characterized by disturbances of milk secretion. It is not necessarily related to pregnancy that is observed in females and can be observed in males.					
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 characterized by abnormally heavy vaginal bleeding 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 characterized 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 characterized 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 characterized 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 characterized by tearing or disruption of the ovarian tissue.					
Ovulation pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in one side of the abdomen between menstrual cycles, around the time of the discharge of the ovum from the ovarian follicle.					
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 characterized by a reduction in the strength of the muscles of the pelvic floor.					
Pelvic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the pelvis.					
Penile pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the penis.					
Perineal 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 area between the genital organs and the anus.					
Premature menopause	-	-	Present	-	-
Definition: A disorder characterized by ovarian failure before the age of 40. Symptoms include hot flashes, 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

Reproductive system and breast disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A disorder characterized by bleeding from the prostate gland.					
Prostatic obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by compression of the urethra secondary to enlargement of the prostate gland. This results in voiding difficulties (straining to void, slow urine stream, and incomplete emptying of the bladder).					
Prostatic 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 prostate gland.					
Scrotal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation 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 characterized 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 characterized by blockage of the normal flow of the contents of the spermatic cord.					
Testicular disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic but not interfering with urination or sexual activities; intervention not indicated; limiting instrumental ADL	Severe symptoms; interfering with urination or sexual function; limiting self care ADL; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by involvement of the testis.					
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 characterized by bleeding from the testis.					
Testicular 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 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 characterized by an abnormal communication 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 characterized 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 characterized by blockage of the uterine outlet.					
Uterine 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 uterus.					
Vaginal discharge	Mild vaginal discharge (greater than baseline for patient)	Moderate to heavy vaginal discharge; use of perineal pad or tampon indicated	-	-	-
Definition: A disorder characterized by vaginal secretions. Mucus produced by the cervical glands is discharged from the vagina naturally, especially during the childbearing years.					
Vaginal dryness	Mild vaginal dryness not interfering with sexual function	Moderate vaginal dryness interfering with sexual function or causing frequent discomfort	Severe vaginal dryness resulting in dyspareunia or severe discomfort	-	-
Definition: A disorder characterized by an uncomfortable feeling of itching and burning in the vagina.					

Reproductive system and breast 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 characterized 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 characterized 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 characterized by inflammation involving the vagina. Symptoms may include redness, edema, marked discomfort and an increase in vaginal discharge.					
Vaginal obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by blockage of vaginal canal.					
Vaginal 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 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 characterized 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 characterized by a narrowing of the vaginal canal.					
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 characterized by involuntary spasms of the pelvic floor muscles, resulting in pathologic tightness of the vaginal wall during penetration such as during sexual intercourse.					
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

Respiratory, thoracic and mediastinal 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 characterized by progressive and life-threatening pulmonary distress in the absence of an underlying pulmonary condition, usually following major trauma or surgery.					
Allergic rhinitis	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by an inflammation of the nasal mucous membranes caused by an IgE-mediated response to external allergens. The inflammation may also involve the mucous membranes of the sinuses, eyes, middle ear, and pharynx. Symptoms include sneezing, nasal congestion, rhinorrhea and itching.					
Apnea	-	-	Present; medical intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by cessation of breathing.					
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 characterized by inhalation of solids or liquids into the lungs.					
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 characterized by the collapse of part or the entire lung.					
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 characterized by an abnormal communication between the bronchus and another 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 characterized by blockage of a bronchus passage, most often by bronchial secretions 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
Definition: A disorder characterized by a narrowing of the bronchial tube.					
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 characterized by an abnormal communication between a bronchus and the pleural cavity.					
Bronchopulmonary 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 characterized by bleeding from the bronchial wall and/or lung parenchyma.					

Respiratory, thoracic and mediastinal disorders					
	Grade				
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 characterized by a sudden contraction of the smooth muscles of the bronchial wall.					
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 characterized by milky pleural effusion (abnormal collection of fluid) resulting from 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 characterized by sudden, often repetitive, spasmodic contraction of the thoracic cavity, resulting in violent release of air from the lungs and usually accompanied by a distinctive sound.					
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 characterized 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 characterized 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 characterized by repeated gulp sounds that result from an involuntary opening and closing of the glottis. This is attributed to a spasm of the diaphragm.					
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 characterized by harsh and raspy voice arising 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
Definition: A disorder characterized by a decrease in the level of oxygen in the body.					
Laryngeal 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
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the larynx.					
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 characterized 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 characterized by bleeding from the larynx.					
Laryngeal inflammation	Mild sore throat; raspy voice	Moderate sore throat; analgesics indicated	Severe throat pain; endoscopic intervention indicated	-	-
Definition: A disorder characterized by an inflammation involving the larynx.					

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 characterized by an inflammation involving the mucous membrane of the larynx.					
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 characterized by blockage of the laryngeal airway.					
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
Definition: A disorder characterized by a narrowing of the laryngeal airway.					
Laryngopharyngeal dysesthesia	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 characterized by an uncomfortable persistent sensation in the area of the laryngopharynx.					
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 characterized by paroxysmal spasmodic muscular contraction of the vocal cords.					
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 characterized by bleeding from the mediastinum.					
Nasal congestion	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Associated with bloody nasal discharge or epistaxis	-	-
Definition: A disorder characterized by obstruction of the nasal passage due to mucosal edema.					
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 characterized by an abnormal communication between the pharynx and another organ or anatomic site.					
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 characterized by bleeding from the pharynx.					
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 characterized by an inflammation involving the mucous membrane of the pharynx.					
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 characterized 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 characterized by a narrowing of the pharyngeal airway.					
Pharyngolaryngeal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation 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	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by an increase in amounts of fluid within the pleural cavity. Symptoms include shortness of breath, cough and marked chest discomfort.					
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 characterized by bleeding from the pleural cavity.					
Pleuritic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the pleura.					
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
Definition: A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma.					
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 characterized 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 characterized by excessive mucous secretion in the back of the nasal cavity or throat, causing sore throat and/or coughing.					
Productive cough	Occasional/minimal production of sputum with cough	Moderate sputum production; limiting instrumental ADL	Persistent or copious production of sputum; limiting self care ADL	-	-
Definition: A disorder characterized by expectorated secretions upon coughing.					
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 characterized by accumulation of fluid in the lung tissues that causes a disturbance 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 characterized by the replacement of the lung tissue by connective tissue, leading to progressive dyspnea, respiratory 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

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Definition: A disorder characterized by an abnormal communication between the lung and another organ 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 characterized by an increase in pressure within 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 characterized by impaired gas exchange by the respiratory system resulting in hypoxemia and a decrease in oxygenation of the tissues that may be associated with an increase in arterial levels of carbon dioxide.					
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 characterized by weight gain, dyspnea, pleural and pericardial effusions, leukocytosis and/or renal failure originally described in patients treated with all-trans retinoic acid.					
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 characterized by involvement of the paranasal 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 characterized by cessation of breathing for short periods during sleep.					
Sneezing	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized 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 characterized 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 characterized by a high pitched breathing sound due to laryngeal or upper airway 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 characterized by an abnormal communication between the trachea and another 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
Definition: A disorder characterized by an inflammation involving the mucous membrane of the trachea.					
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 characterized by a narrowing of the trachea.					

Respiratory, thoracic and mediastinal 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 characterized by a change in the sound and/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 characterized by a high-pitched, whistling sound during breathing. It results from the narrowing or obstruction of the 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 cover the hair loss but it does not require a wig or hair piece to camouflage	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; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by a decrease in density of hair compared to normal for a given individual 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 characterized by an abnormal body smell resulting from the growth of bacteria on the body.					
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 characterized by inflammation of the skin characterized by the presence of bullae which are filled with fluid.					
Dry 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 characterized 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 characterized by target lesions (a pink-red ring around a pale center).					
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 characterized by generalized inflammatory erythema and exfoliation. The inflammatory process involves > 90% of 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	-	-
Definition: A disorder characterized by shrinking of adipose tissue.					
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 characterized by the presence of excess hair growth in women in anatomic sites where growth is considered to be a secondary male characteristic and under androgen control (beard, moustache, chest, abdomen)					
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	-	-
Definition: A disorder characterized by excessive perspiration.					

Skin and subcutaneous tissue disorders					
	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 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 destructive means of hair removal to camouflage; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by hair density or length beyond the accepted limits of normal in a particular body region, for a particular age or race.					
Hypohidrosis	-	Symptomatic; limiting instrumental ADL	Increase in body temperature; limiting self care ADL	Heat stroke	Death
Definition: A disorder characterized by reduced sweating.					
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 characterized by hypertrophy of the subcutaneous adipose tissue at the site of multiple subcutaneous injections of insulin.					
Nail discoloration	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characterized by a change in the color of the nail plate.					
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 characterized by loss of all or a portion of the nail.					
Nail ridging	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characterized 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 characterized by marked discomfort sensation in the skin.					
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	-	-
Definition: A disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of the hands or the soles of the feet.					
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 characterized by swelling due to an excessive 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
Definition: A disorder characterized by an increase in sensitivity of the skin to light.					

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 characterized 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	-	-
Definition: A disorder characterized by hemorrhagic areas of the skin and mucous membrane. Newer lesions appear reddish in color. Older lesions are usually a darker purple color and eventually become a brownish-yellow 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; life-threatening consequences	Death
Definition: A disorder characterized by an eruption of papules and pustules, typically appearing in face, 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	-	-
Definition: A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbillform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and associated with pruritus.					
Scalp pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation 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 characterized by the degeneration and thinning of the epidermis and dermis.					
Skin hyperpigmentation	Hyperpigmentation covering <10% BSA; no psychosocial impact	Hyperpigmentation covering >10% BSA; associated psychosocial impact	-	-	-
Definition: A disorder characterized 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 characterized 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 characterized by an area of hardness in the skin.					
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
Definition: A disorder characterized by circumscribed, inflammatory and necrotic erosive lesion on the skin.					

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 characterized by less than 10% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.					
Telangiectasia	Telangiectasias covering <10% BSA	Telangiectasias covering >10% BSA; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by local dilatation of small vessels resulting in red discoloration of 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 characterized by greater than 30% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the 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 at age 40 - 45 years of age	Menopause occurring before age 40 years of age	-	-
Definition: A disorder characterized by the permanent cessation of menses, usually defined by 12 consecutive months of amenorrhea in 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 procedures - 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

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
Definition: A disorder characterized by leakage of intravascular fluids into the extravascular space. This syndrome is observed in patients who demonstrate a state of generalized leaky capillaries following shock syndromes, low-flow states, ischemia-reperfusion injuries, toxemias, medications, or poisoning. It can lead to generalized edema and multiple organ 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 characterized by episodic reddening of the face.					
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 characterized by a localized collection of blood, usually clotted, in an organ, space, or tissue, due to a break in the 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 characterized by an uncomfortable and temporary sensation of intense body warmth, flushing, sometimes accompanied 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 WNL; monotherapy indicated Pediatric: recurrent or persistent (>=24 hrs) BP >ULN; monotherapy indicated	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 characterized by a pathological increase in blood pressure; a repeatedly elevation in the blood pressure exceeding 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 characterized by a blood pressure that is below the normal expected for an individual 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
Definition: A disorder characterized by the loss of lymph fluid into the surrounding tissue or body cavity.					
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 characterized 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 characterized by a cystic lesion containing lymph.					
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 characterized by impaired circulation to an extremity.					
Phlebitis	-	Present	-	-	-
Definition: A disorder characterized by inflammation of the wall of a vein.					
Superficial thrombophlebitis	-	Present	-	-	-
Definition: A disorder characterized by a blood clot and inflammation involving a superficial vein of the extremities.					

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 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 characterized by occlusion of a vessel by a thrombus 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 characterized by inflammation involving the wall 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 characterized 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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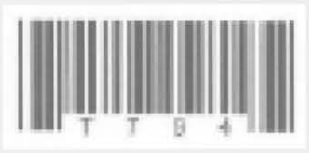

APPENDIX 2. PEMPHIGUS DISEASE AREA INDEX (PDAI)

Pemphigus Disease Area Index (PDAI)

Skin	Activity		Damage
Anatomical Locatio	Erosion/Blisters or new 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 > 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	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 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 membrane

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	

Total Activity Score: ☐ **Total Damage Score** ☐

APPENDIX 3. AUTOIMMUNE BULLOUS DISEASE QUALITY OF LIFE (ABQOL) QUESTIONNAIRE

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 which *blistering disease treatments* affect your quality of life.

Please choose an option from the right hand column which most closely correlates to how you felt *within the last week*.

Please time your survey in minutes and seconds – start time _____ AM/PM

1. In regards to your blistering disease, does your skin burn, sting or hurt in any way?	○ All the time ○ Sometimes ○ Occasionally ○ Not at all
2. In regards to your blistering disease, does your skin itch?	○ All the time ○ Sometimes ○ Occasionally ○ Not at all
3. Have you had to change your clothing because of your blistering disease?	○ I have to be very careful with how tight 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 ○ I have never had this problem
5. Do you have difficulty bathing or showering because of your blistering disease?	○ All the time ○ Sometimes ○ Occasionally ○ Not at all

6. In regards to your blistering disease, does your mouth have erosions which are painful?	○ All the time ○ Sometimes ○ Occasionally ○ Not at all
7. In regards to your blistering disease, do your gums bleed easily?	○ All the time ○ Sometimes ○ Occasionally ○ Not at all
8. 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

DERMATOLOGY SURVEY

This survey concerns the skin condition which has bothered you the most during the past four weeks.

Skindex29
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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	☐2	☐3	☐4	☐5
2. My skin condition affects how well I sleep	☐1	☐2	☐3	☐4	☐5
3. I worry that my skin condition may be serious	☐1	☐2	☐3	☐4	☐5
4. My skin condition makes it hard to work or do hobbies	☐1	☐2	☐3	☐4	☐5
5. My skin condition affects my social life	☐1	☐2	☐3	☐4	☐5
6. My skin condition makes me feel depressed	☐1	☐2	☐3	☐4	☐5
7. My skin condition burns or stings	☐1	☐2	☐3	☐4	☐5
8. I tend to stay at home because of my skin condition	☐1	☐2	☐3	☐4	☐5
9. I worry about getting scars from my skin condition	☐1	☐2	☐3	☐4	☐5
10. My skin itches	☐1	☐2	☐3	☐4	☐5
11. My skin condition affects how close I can be with those I love	☐1	☐2	☐3	☐4	☐5
12. I am ashamed of my skin condition	☐1	☐2	☐3	☐4	☐5
13. I worry that my skin condition may get worse	☐1	☐2	☐3	☐4	☐5
14. I tend to do things by myself because of my skin condition	☐1	☐2	☐3	☐4	☐5
15. I am angry about my skin condition	☐1	☐2	☐3	☐4	☐5
16. Water bothers my skin condition (bathing, washing hands)	☐1	☐2	☐3	☐4	☐5
17. My skin condition makes showing affection difficult	☐1	☐2	☐3	☐4	☐5
18. I worry about side-effects from skin medications / treatments	☐1	☐2	☐3	☐4	☐5
19. My skin is irritated	☐1	☐2	☐3	☐4	☐5
20. My skin condition affects my interactions with others	☐1	☐2	☐3	☐4	☐5

Please turn to next page

Skindex29

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	☐2	☐3	☐4	☐5
22. My skin condition is a problem for the people I love . . .	☐1	☐2	☐3	☐4	☐5
23. I am frustrated by my skin condition	☐1	☐2	☐3	☐4	☐5
24. My skin is sensitive	☐1	☐2	☐3	☐4	☐5
25. My skin condition affects my desire to be with people . .	☐1	☐2	☐3	☐4	☐5
26. I am humiliated by my skin condition	☐1	☐2	☐3	☐4	☐5
27. My skin condition bleeds	☐1	☐2	☐3	☐4	☐5
28. I am annoyed by my skin condition	☐1	☐2	☐3	☐4	☐5
29. My skin condition interferes with my sex life	☐1	☐2	☐3	☐4	☐5
30. My skin condition makes me tired	☐1	☐2	☐3	☐4	☐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
Sponsor:	Syntimmune, Inc. 116 Huntington Avenue Suite 301 Boston, MA 02116
Medical Monitor:	PPD Wallace House 17-21 Maxwell Place Stirling, Scotland FK81JU Mobile Phone: PPD Office Phone: PPD ext. PPD

Original Protocol	18 January 2017
1.0	21 March 2017
2.0	12 April 2017
3.0	10 October 2017
4.0	08 June 2018

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/m^2) 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 Number and Title	Description of Change
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: o Safety assessments o Pharmacokinetics o Pharmacodynamics/Activity o Immunogenicity o 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. o 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 $\leq$ 30 mg/kg and the number of subjects reduced from 8 to 4. • Cohort 3 has been added with $\leq$ 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 Events	Table 3 (Cohort 2) • Efforts were made to simplify the study of events to reduce subject and site burden and increase flexibility with visit scheduling, as described below: o A total of 7 visits have been removed (Days 1, 2, 5, 12, 19, 29, and 20). o Day 33 has been changed to Day 35 to shift to a weekly visit schedule out to 1 month after the final dose. o 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. o Pemphigus Disease Area Index (PDAI), physical examination, and anti-desmoglein (1 and 3) antibody titers are being done at every visit. o Tetanus and Varicella Zoster testing will now be done at set timepoints (Baseline, Day 56, and Day 112). o 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. o 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. o Assessments at the mid-point of dosing and the final dose (major visits) align with Cohort 2 (Table 3). o 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 Objectives and Endpoints	• Study objectives and endpoints have not fundamentally changed but have been rewritten to more closely align with industry standards. • An objective and endpoint have been added for dose selection to define criteria to select a dose for future clinical testing. • Edits have been made to ensure each objective has a corresponding endpoint and vice versa.

	• 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 Drug	Description of SYNT001 • Windows for the SYNT001 infusion duration (±15 minutes) have been 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 Design	The study design has been updated to reflect changes in dose, number of doses and timing of DEC reviews for Cohorts 2 and 3 and adding optional 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 Population	Target 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. ○ 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/m^2. • #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. o The timing windows for Cohorts 2, 3, and optional Cohort 4 were added. o 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.

	• #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.
Section 9, Study Rules	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. 116 Huntington Avenue Suite 301 Boston, MA 02116
Medical Monitor:	PPD 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
Amendment 4.0	08 June 2018
Amendment 5.0	18 September 2018

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

Syntimmune, Inc.

18 SEPT 2018

Date of Signature

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 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 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.

<table>
<tr><td>Study objectives and endpoints</td><td>The study objectives and their corresponding endpoints (primary, secondary, and exploratory) are detailed below.
<table>
<tr><th>Primary Objectives</th><th>Primary Endpoints</th></tr>
<tr><td>Safety: To evaluate the safety of IV infusions of SYNT001 at different dose levels and dosing regimens in subjects with pemphigus (vulgaris or foliaceus)</td><td>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</td></tr>
<tr><td>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)</td><td>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)</td></tr>
<tr><th>Secondary Objectives</th><th>Secondary Endpoints</th></tr>
<tr><td>To evaluate the efficacy of doses of SYNT001 at different dose levels and dosing regimens on pharmacodynamics (PD) biomarkers</td><td>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</td></tr>
</table></td></tr>
</table>

	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 anti-desmoglein 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:

		• 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)

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.

Table 1. Cohort Overview

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[c]	Weekly[c]
		Maintenance: 10 mg/kg[c]	5[c]	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 entry criteria	**Inclusion criteria:** Subjects 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 >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 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 ± 15 minutes Investigators may adjust the duration of the infusion if needed to improve tolerability.

<table>
<tr><td>Control, dose, and route of administration</td><td>Not applicable</td></tr>
<tr><td>Duration of subject participation</td><td>The duration of subject participation for each cohort is as follows:
<table>
<tr><th rowspan="2">Cohort</th><th rowspan="2">Screening</th><th rowspan="2">Treatment</th><th rowspan="2">Follow-up</th><th colspan="2">Maximum Total</th></tr>
<tr><th>Days</th><th>Weeks</th></tr>
<tr><td>1</td><td>≤14 days</td><td>28 days</td><td>84 days</td><td>126 days</td><td>18 weeks</td></tr>
<tr><td>2</td><td>≤14 days</td><td>84 days</td><td>56 days</td><td>154 days</td><td>22 weeks</td></tr>
</table></td></tr>
<tr><td>Permitted and prohibited concomitant treatments</td><td>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 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, histamine$_2$ (H_2) blockers (eg, ranitidine, famotidine).
6. Low-strength topical 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).
9. Stable regimen of the following systemic immunosuppressants: azathioprine, mycophenolate mofetil, low-dose 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 infusion reaction to SYNT001)
5. Any investigational drug or device</td></tr>
</table>

	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 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 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

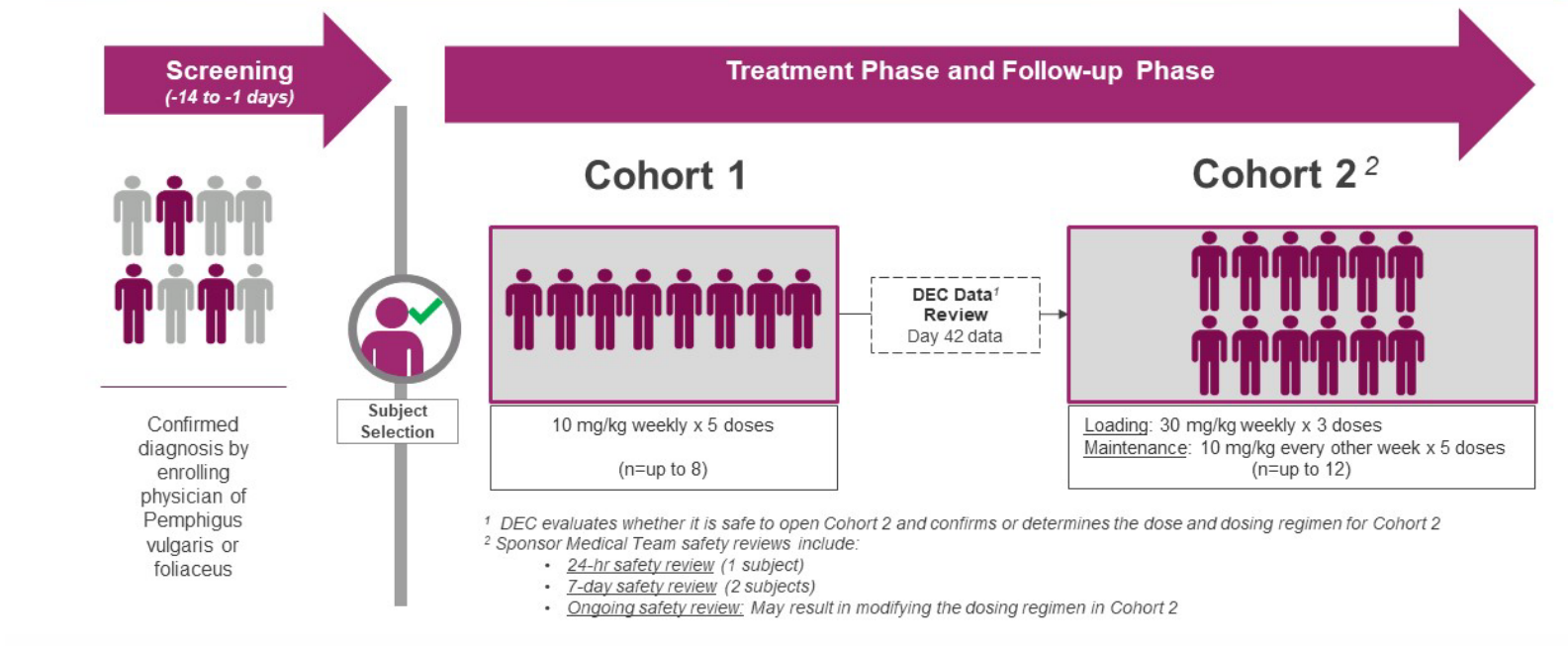

Table 2. Study Assessments for Cohort 1

	Screening	Treatment Period															Follow-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 (±1 h)**	**2 (±2 h)**	**5[p] (±4 h)**	**7 (±6 h)**	**12[p] (±6 h)**	**14 (±6 h)**	**19[p] (±6 h)**	**21 (±6 h)**	**28 (±6 h)**	**29 (±1 h)**	**30 (±2 h)**	**33 (±4 h)**	**42 (±3 d)**	**56 (±5 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
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	X[q]
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[l]		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 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 = 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.

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.

l. **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	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)[l]	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.

l. **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
AUC_{0-24}	area under the serum concentration-time curve from pre-dose ($time_0$) to 24 hours post-dose
$AUC_{0-\infty}$	area under the serum concentration-time curve from pre-dose ($time_0$) 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
H_2	$histamine_2$

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

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 ($AUC_{0-\infty}$), (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

	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: • 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 ± 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 (2ºC to 8ºC/36ºF to 46ºF) 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.

Table 4. Cohort Overview

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[c]	Weekly[c]
		Maintenance: 10 mg/kg[c]	5[c]	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 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, ≤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 ≥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 [≤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/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.
[b] Urine IgG collected in Cohort 1 only.

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.

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 (≥25) (Shimizu et al., 2014). The Investigator will determine a PDAI score as follows: 0 to 250 points for disease activity (≤120 for skin, ≤10 for scalp, and ≤120 for mucosa), and 0 to 13 points for damage (≤12 for skin and ≤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 ± 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

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, histamine$_2$ (H_2) 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).

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.

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

- 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 ± 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 ± 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 ± 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 (± 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 (± 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 (± 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 (± 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 (± 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 (± 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 ± 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 ± 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 ± 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 (± 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 (± 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 (± 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 ± 1 day), 42, 56, 70, and 84 (all ± 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
  - AECA
  - 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 (± 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 (± 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 (± 5 days) and Cohort 2 Days 91 and 140 (± 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.

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.

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)
    - 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, 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**
- **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:

Medpace Clinical Safety
Medpace SAE hotline:
Telephone: PPD dial P or PPD dial P
Facsimile: PPD or PPD
e-mail: PPD

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

Medical Safety Contact

PPD
Phone (EU): PPD extension PPD
Mobile phone: PPD
Email: PPD

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

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

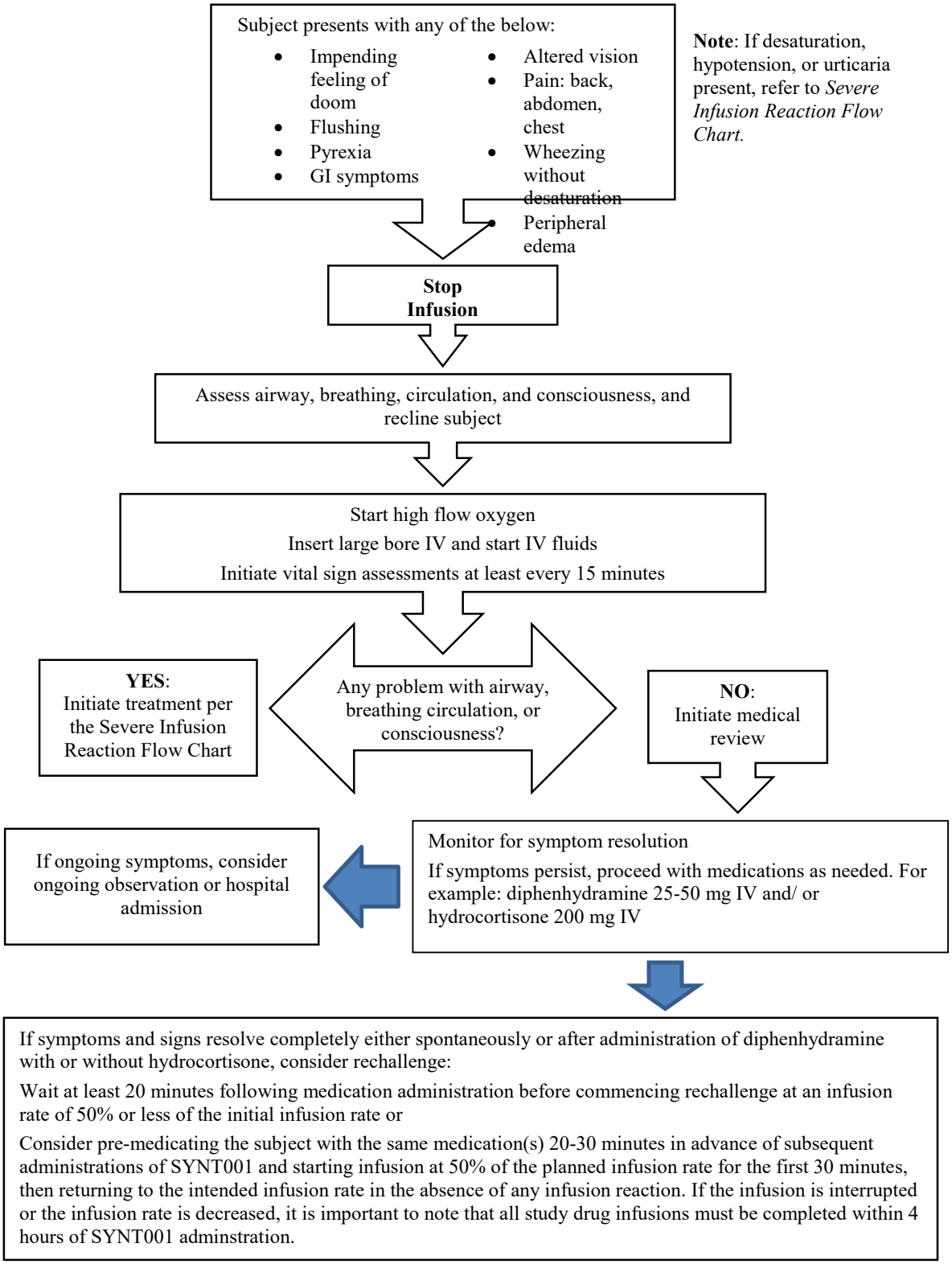

Figure 3. Management of Severe (Grade 3 or Higher) Infusion Reactions

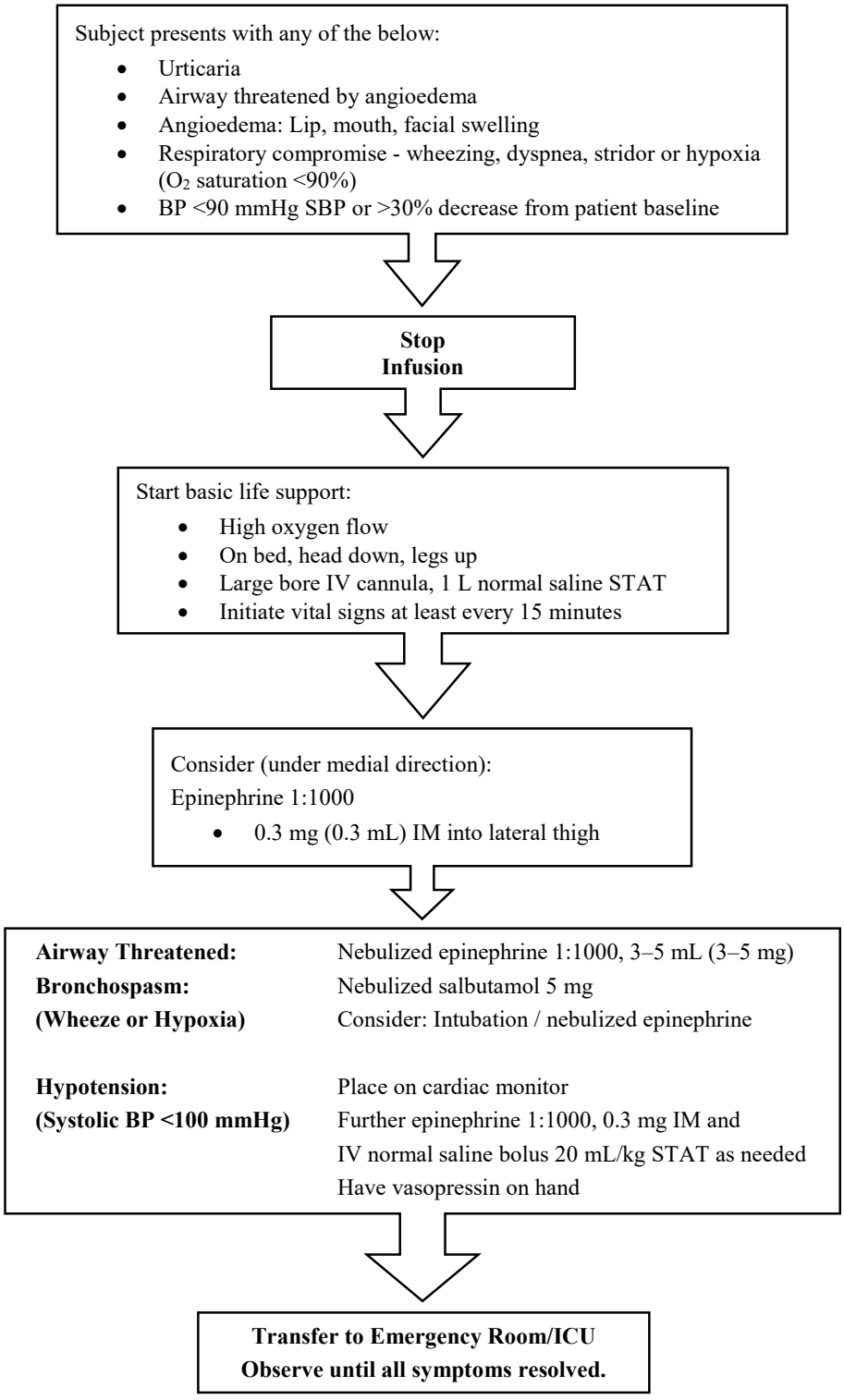

Table 8. Grading and Management of Allergic or Infusion-Related Reactions

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 (eg, antihistamines, non-steroidal anti-inflammatory 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.

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-

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 ≥60% and ≤90% from baseline and (ii) a PDAI total activity score of ≥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

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 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

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.

Table 9. Study Administrative Structure

Sponsor Contact and Medical Director:	PPD PPD Phone: PPD Email: PPD
Medical Monitor:	PPD Medpace Wallace House Stirling, Scotland FK81JU Phone: PPD extension PPD Email: PPD
Study Monitoring:	Medpace 5375 Medpace Way Cincinnati, OH 45227 USA Phone (Main): PPD Email: PPD

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

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

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 *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 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).

CONTENTS

Blood and lymphatic system disorders					
	Grade				
Adverse Event	1	2	3	4	5
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	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
Definition: A disorder characterized by an reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.					
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 characterized by the inability of the bone marrow to produce hematopoietic elements.					
Disseminated intravascular coagulation	-	Laboratory findings with no bleeding	Laboratory findings and bleeding	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by systemic pathological activation of blood clotting mechanisms which results in clot formation throughout the body. There is an increase in the risk of hemorrhage as the body is depleted of platelets and coagulation factors.					
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 characterized by an ANC <1000/mm3 and 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.					
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 characterized by laboratory test results that indicate widespread erythrocyte cell 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 characterized by a form of thrombotic microangiopathy with renal failure, hemolytic anemia, and severe thrombocytopenia.					
Leukocytosis	-	-	>100,000/mm3	Clinical manifestations of leucostasis; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate an increased number of white blood cells in the blood.					
Lymph node 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 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 spleen.					
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
Definition: A disorder characterized by the presence of microangiopathic hemolytic anemia, thrombocytopenic purpura, fever, renal abnormalities and neurological abnormalities such as seizures, hemiplegia, and visual disturbances. It is an acute or subacute condition.					
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
Definition: A disorder characterized by signs and symptoms related to acute ischemia of the myocardium secondary to coronary artery disease. The clinical presentation covers a spectrum of heart diseases from unstable angina to myocardial infarction.					
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 characterized by a defect in aortic valve function or structure.					
Asystole	Periods of asystole; non-urgent medical management indicated	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia without cardiac electrical activity. Typically, this is accompanied by cessation of the 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 characterized by a dysrhythmia without discernible P waves and an irregular ventricular response due to multiple reentry circuits. The rhythm disturbance originates above the ventricles.					
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 characterized by a dysrhythmia with organized rhythmic atrial contractions with a rate of 200-300 beats per minute. The rhythm disturbance originates in the atria.					
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 characterized by a dysrhythmia with complete 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	-	-	-
Definition: A disorder characterized by a dysrhythmia with a delay in the time required for the conduction of an electrical impulse through the atrioventricular (AV) node beyond 0.2 seconds; prolongation of the PR interval greater than 200 milliseconds.					
Cardiac arrest	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by cessation of the pumping function of the heart.					
Chest pain - cardiac	Mild pain	Moderate pain; limiting instrumental ADL	Pain at rest; limiting self care ADL	-	-
Definition: A disorder characterized by substernal discomfort due to insufficient myocardial oxygenation.					
Conduction disorder	Mild symptoms; intervention not indicated	Moderate symptoms	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized 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 characterized by a thickened and fibrotic pericardial sac; these fibrotic changes impede normal myocardial function by restricting myocardial muscle 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 support)	Death
Definition: A disorder characterized by the inability of the heart to pump blood at an adequate volume to meet tissue metabolic requirements, or, the ability to do so only at an elevation in the filling pressure.					

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
Definition: A disorder characterized by failure of the left ventricle to produce adequate output despite an increase in distending pressure and in end-diastolic volume. Clinical manifestations mayinclude dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.					
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 characterized by a defect in mitral valve function 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
Definition: A disorder characterized by a dysrhythmia with relatively constant PR interval prior to the block of an atrial impulse. This is the result of intermittent failure of atrial electrical impulse conduction through the atrioventricular (AV) node to the ventricles.					
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
Definition: A disorder characterized by a dysrhythmia with a progressively lengthening PR interval prior to the blocking of an atrial impulse. This is the result of intermittent failure of atrial electrical impulse conduction through the atrioventricular (AV) node to the ventricles.					
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 characterized by gross necrosis of the myocardium; this is due to an interruption 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 characterized by inflammation of the muscle tissue of the heart.					
Palpitations	Mild symptoms; intervention not indicated	Intervention indicated	-	-	-
Definition: A disorder characterized by an unpleasant sensation of irregular and/or forceful beating of 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 characterized by a dysrhythmia with abrupt onset and sudden termination of atrial contractions with a rate of 150-250 beats per minute. The rhythm disturbance originates in the atria.					
Pericardial effusion	-	Asymptomatic effusion size small to moderate	Effusion with physiologic consequences	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by fluid collection within the pericardial sac, usually due to inflammation.					
Pericardial tamponade	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in intrapericardial pressure due to the collection of blood or fluid in the pericardium.					
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
Definition: A disorder characterized by irritation to the layers of the pericardium (the protective sac around the heart).					

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 characterized by a defect in pulmonary valve function or structure.					
Restrictive cardiomyopathy	-	-	Symptomatic heart failure or other cardiac symptoms, responsive to intervention	Refractory heart failure or other poorly controlled cardiac symptoms	Death
Definition: A disorder characterized by an inability of the ventricles to fill with blood because the myocardium (heart muscle) stiffens and loses its flexibility.					
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 characterized by impairment of right ventricular function associated with low ejection fraction and a decrease in motility 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
Definition: A disorder characterized by a dysrhythmia with alternating periods of bradycardia and atrial tachycardia accompanied by syncope, fatigue and dizziness.					
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 characterized by a dysrhythmia with a heart rate 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 characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates in the sinus node.					
Supraventricular tachycardia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates above the ventricles.					
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 characterized by a defect in tricuspid valve function 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 characterized by a dysrhythmia that originates in the ventricles.					
Ventricular fibrillation	-	-	-	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia without discernible QRS complexes due to rapid repetitive excitation of myocardial fibers without coordinated contraction of the ventricles.					
Ventricular tachycardia	-	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates distal to the bundle 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 characterized by the presence of an accessory conductive pathway between the atria and the ventricles that causes premature ventricular activation.					
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 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 characterized by a sensation of marked discomfort 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 characterized by inflammation, swelling and redness to the outer ear and ear canal.					
External ear 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 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 aids; threshold shift >20 dB at 3 kHz and above in at least one ear; additional speech-language related services indicated.	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.	-
Definition: A disorder characterized by partial or complete loss of the ability to detect or understand sounds resulting from damage to ear structures.					
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
Definition: A disorder characterized by inflammation (physiologic response to irritation), swelling and redness to the middle ear.					
Tinnitus	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by noise in the ears, such as ringing, buzzing, roaring or clicking.					
Vertigo	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation as if the external world were revolving around the patient (objective vertigo) or as if he himself were revolving in space (subjective vertigo).					
Vestibular disorder	-	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dizziness, imbalance, nausea, 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	Moderate symptoms; medical intervention indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder that occurs when the adrenal cortex does not produce enough of the hormone cortisol and in some cases, the hormone aldosterone. It may be due to a disorder of the adrenal cortex as in Addison's disease or primary adrenal insufficiency.					
Cushingoid	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms, medical intervention or hospitalization indicated	-	-
Definition: A disorder characterized by signs and symptoms that resemble Cushing's disease or syndrome: buffalo hump obesity, striations, adiposity, hypertension, diabetes, and osteoporosis, usually due to exogenous corticosteroids.					
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 characterized by unusually late sexual maturity.					
Growth accelerated	-	>= +2 SD (standard deviation) above mid parental height or target height	-	-	-
Definition: A disorder characterized by greater growth than expected for age.					
Hyperparathyroidism	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by an increase in production of parathyroid hormone by the parathyroid glands. This results in hypercalcemia (abnormally high levels of calcium in the blood).					
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 characterized by excessive levels of thyroid hormone in the body. Common causes include an overactive thyroid gland or thyroid hormone overdose.					
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 characterized by a decrease in production of parathyroid hormone by the parathyroid 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 characterized by a decrease in production of thyroid hormone by the thyroid gland.					
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 characterized by unusually early development of secondary sexual features; the onset of sexual maturation begins usually before age 8 for girls and before age 9 for boys.					
Virilization	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by inappropriate masculinization occurring in a female or prepubertal 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 disorders					
	Grade				
Adverse Event	1	2	3	4	5
Blurred vision	Intervention not indicated	Symptomatic; limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by visual perception of unclear or fuzzy images.					
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., cataract surgery)	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by partial or complete opacity of the crystalline lens of one or both eyes. This results in a decrease in visual acuity and eventual blindness if untreated.					
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 characterized by inflammation, swelling and redness to the conjunctiva of the eye.					
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 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	Symptomatic; multiple agents indicated; limiting instrumental ADL	Decrease in visual acuity (<20/40); limiting self care ADL	-	-
Definition: A disorder characterized 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 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 characterized by a sensation of marked discomfort in the eye.					
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 characterized by impaired eyelid function.					
Flashing lights	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by a sudden or brief burst of light.					
Floaters	Symptomatic but not limiting ADL	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.					
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 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	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 characterized by inflammation to the cornea of the eye.					
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 characterized by an inability to see clearly in dim light.					

Eye disorders					
	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	-
Definition: A disorder characterized by involvement of the optic nerve (second cranial nerve).					
Papilledema	Asymptomatic; no visual field defects	Symptomatic decline in 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 characterized by swelling around the optic disc.					
Photophobia	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by fear and avoidance of 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 characterized by the separation of the inner retina layers from the underlying 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 characterized by a small laceration of the retina, this occurs when the vitreous separates from the retina. Symptoms include flashes and floaters.					
Retinal vascular disorder	-	Topical medication indicated	Intravitreal medication; operative intervention indicated	-	-
Definition: A disorder characterized by pathological retinal blood vessels that adversely affects 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 involving 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 characterized by involvement of the sclera of the eye.					
Uveitis	Asymptomatic; clinical or diagnostic observations only	Anterior uveitis; medical intervention indicated	Posterior or pan-uveitis	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by inflammation to the uvea of the eye.					
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 characterized by blood extravasation into the vitreous humor.					
Watering eyes	Intervention not indicated	Intervention indicated	Operative intervention indicated	-	-
Definition: A disorder of excessive tearing in the eyes; it can be caused by overproduction 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 disorders					
	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 characterized by swelling of the abdomen.					
Abdominal 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 abdominal region.					
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 characterized 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 characterized by bleeding from the anal region.					
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 characterized 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
Definition: A disorder characterized by a necrotic process occurring in the anal region.					
Anal 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 anal region.					
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 characterized 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 characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the anal canal.					
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 characterized by accumulation of serous or hemorrhagic 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 characterized by subject-reported feeling of uncomfortable fullness of the abdomen.					
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 characterized 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	-	-
Definition: A disorder characterized by inflammation of the lip.					

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
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 characterized 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 characterized 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 characterized by bleeding from the colon.					
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
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents in the colon.					
Colonic perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the colonic wall.					
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 characterized 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 characterized by a circumscribed, inflammatory 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 characterized by irregular and infrequent or difficult 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 characterized by the decay of a tooth, in which 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 characterized by frequent and watery bowel movements.					
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	-	-
Definition: A disorder characterized by reduced salivary flow in the oral cavity.					

Gastrointestinal disorders					
	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 characterized by an abnormal communication between the duodenum and another 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 characterized by bleeding from the duodenum.					
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 characterized 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 characterized by a rupture in the duodenal wall.					
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 characterized 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 characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the duodenal wall.					
Dyspepsia	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; surgical intervention indicated	-	-
Definition: A disorder characterized by an uncomfortable, often painful feeling in the stomach, resulting from impaired digestion. Symptoms include burning stomach, bloating, heartburn, nausea and vomiting.					
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 characterized by difficulty in swallowing.					
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 characterized by inflammation of the small and 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 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	Life-threatening consequences; urgent intervention indicated	Death
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 or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the esophagus.					

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 characterized by a necrotic process occurring 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 characterized by blockage of the normal flow of the contents in the esophagus.					
Esophageal 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 esophageal region.					
Esophageal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the wall of the esophagus.					
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 characterized 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 characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the esophageal 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 characterized by bleeding from esophageal varices.					
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 characterized by inflammation of the esophageal wall.					
Fecal incontinence	Occasional use of pads required	Daily use of pads required	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by inability to control the escape of stool from the rectum.					
Flatulence	Mild symptoms; intervention not indicated	Moderate; persistent; psychosocial sequelae	-	-	-
Definition: A disorder characterized by a state of excessive gas in the alimentary canal.					
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 characterized by an abnormal communication between the stomach and another organ or anatomic site.					
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 characterized by bleeding from the gastric wall.					
Gastric 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 characterized by a necrotic process occurring in the gastric wall.					

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Gastric perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the stomach wall.					
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 characterized 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
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the stomach.					
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 characterized by inflammation of the stomach.					
Gastroesophageal reflux disease	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; surgical intervention indicated	-	-
Definition: A disorder characterized by reflux of the gastric and/or duodenal contents into the distal esophagus. It is chronic in nature and usually caused by incompetence of the lower esophageal sphincter, and may result in injury to the esophageal mucosal. Symptoms include heartburn and acid indigestion.					
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 characterized by an abnormal communication between any part of the gastrointestinal 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 characterized by a sensation of marked discomfort in the gastrointestinal region.					
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 characterized by an incomplete paralysis of the muscles of the stomach wall resulting in delayed emptying of the gastric contents into the small intestine.					
Gingival pain	Mild pain	Moderate pain interfering with oral intake	Severe pain; inability to aliment orally	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the gingival region.					
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 characterized by bleeding from the hemorrhoids.					
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 characterized by the presence of dilated veins in the rectum and surrounding area.					
Ileal 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 characterized by an abnormal communication between the ileum and another organ or anatomic site.					
Ileal 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 characterized by bleeding from the ileal wall.					

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Ileal 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 characterized by blockage of the normal flow of the intestinal contents in the ileum.					
Ileal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the ileal wall.					
Ileal 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 characterized by a narrowing of the lumen of the ileum.					
Ileal 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 characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the ileum.					
Ileus	-	Symptomatic; altered GI function; bowel rest indicated	Severely altered GI function; TPN indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by failure of the ileum to transport intestinal contents.					
Intra-abdominal hemorrhage	-	Medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding in the abdominal cavity.					
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 characterized by an abnormal communication between the jejunum and another 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 characterized by bleeding from the jejunal wall.					
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 characterized by blockage of the normal flow of the intestinal contents in the jejunum.					
Jejunal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized 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 characterized 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 characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the jejunum.					
Lip pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort of the lip.					

Gastrointestinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Lower 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 characterized by bleeding from the lower gastrointestinal 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 characterized by inadequate absorption of nutrients in the small intestine. Symptoms include abdominal marked 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 characterized by inflammation of the oral mucosal.					
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 characterized by a queasy sensation and/or the urge to vomit.					
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 characterized by blockage of the normal flow of the contents in the stomach.					
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 characterized by an abnormal communication between the oral cavity and another 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 characterized by a burning or tingling sensation on the lips, tongue or entire mouth.					
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 characterized by bleeding from the mouth.					
Oral 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 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 characterized 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 characterized by an abnormal communication between the pancreas and another organ or anatomic site.					
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 characterized by bleeding from the pancreas.					
Pancreatic necrosis	-	-	Tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized 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
Definition: A disorder characterized by inflammation of the pancreas.					
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 gingival 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 characterized 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 characterized 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 characterized by an abnormal communication 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 characterized 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 characterized 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 characterized 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 characterized by blockage of the normal flow of the intestinal contents in the rectum.					
Rectal 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 rectal region.					
Rectal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized 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 characterized 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
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the rectum.					

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
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 characterized by bleeding from the retroperitoneal area.					
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 characterized 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 characterized by an abnormal communication between a salivary gland and another 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 characterized 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 characterized 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 characterized by a rupture in the small intestine 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 characterized 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 characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the small intestine.					
Stomach 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 stomach.					
Tooth development disorder	Asymptomatic; hypoplasia of tooth or enamel	Impairment correctable with oral surgery	Maldevelopment with impairment not surgically correctable; disabling	-	-
Definition: A disorder characterized by a pathological process of the teeth occurring during tooth development.					
Tooth discoloration	Surface stains	-	-	-	-
Definition: A disorder characterized by a change in tooth hue or tint.					
Toothache	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 tooth.					

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 characterized 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 characterized by bleeding from the upper gastrointestinal tract (oral cavity, pharynx, 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 characterized by the reflexive act of ejecting the contents of the stomach through 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

General disorders and administration site conditions					
	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 characterized by a sensation of cold that often marks a physiologic response to sweating after a fever.					
Death neonatal	-	-	-	-	Death
Definition: A disorder characterized by cessation of life occurring during 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 characterized by swelling due to excessive fluid 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 characterized by swelling due to excessive fluid accumulation in the upper or lower 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 characterized by swelling due to excessive fluid accumulation in the trunk area.					
Facial 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 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 characterized by a state of generalized weakness with a pronounced inability to summon sufficient energy to accomplish 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 characterized by elevation of the body's temperature above the upper limit of normal.					
Flu like symptoms	Mild flu-like symptoms present	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by a group of symptoms similar to those observed in patients with the flu. It includes fever, chills, body aches, malaise, loss of appetite and dry cough.					
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 characterized by walking difficulties.					
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
Definition: A disorder characterized by an abnormally low body temperature. Treatment is required when the body temperature is 35C (95F) or below.					

General disorders and administration site conditions					
	Grade				
Adverse 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 (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	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.					
Infusion site extravasation	-	Erythema with associated symptoms (e.g., edema, pain, induration, phlebitis)	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by leakage of a pharmacologic or a biologic substance from the infusion site into the surrounding tissue. Signs and symptoms include induration, erythema, swelling, burning sensation and marked discomfort at the infusion site.					
Injection site reaction	Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)	Pain; lipodystrophy; edema; phlebitis	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an intense adverse reaction (usually immunologic) developing at the site of an injection.					
Irritability	Mild; easily consolable	Moderate; limiting instrumental ADL; increased attention indicated	Severe abnormal or excessive response; limiting self care ADL; inconsolable	-	-
Definition: A disorder characterized by an abnormal responsiveness to stimuli or physiological arousal; may be in response to pain, fright, a drug, an emotional situation or a medical condition.					
Localized edema	Localized to dependent areas, no disability or functional impairment	Moderate localized edema and intervention indicated; limiting instrumental ADL	Severe localized edema and intervention indicated; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to excessive fluid accumulation at a specific anatomic site.					
Malaise	Uneasiness or lack of well being	Uneasiness or lack of well being; limiting instrumental ADL	-	-	-
Definition: A disorder characterized by a feeling of general discomfort or uneasiness, an out-of-sorts feeling.					
Multi-organ failure	-	-	Shock with azotemia and acid-base disturbances; significant coagulation abnormalities	Life-threatening consequences (e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic acidosis)	Death
Definition: A disorder characterized by progressive deterioration of the lungs, liver, kidney and clotting mechanisms.					
Neck edema	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	-	-
Definition: A disorder characterized by swelling due to an accumulation of excessive fluid in the neck.					
Non-cardiac chest pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by discomfort in the chest unrelated to a heart disorder.					
Pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by the sensation of marked discomfort, distress or agony.					
Sudden death NOS	-	-	-	-	Death
Definition: An unexpected cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.					
General disorders and administration site conditions - 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

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 characterized by a narrowing of the lumen of the bile duct.					
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 characterized by an abnormal communication between the bile ducts and another 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 characterized by inflammation involving the gallbladder. It may be associated with 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 characterized by an abnormal communication between the gallbladder and another organ or anatomic site.					
Gallbladder necrosis	-	-	-	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring 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
Definition: A disorder characterized by blockage of the normal flow of the contents of the gallbladder.					
Gallbladder 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 gallbladder region.					
Gallbladder perforation	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the gallbladder wall.					
Hepatic failure	-	-	Asterixis; mild encephalopathy; limiting self care ADL	Moderate to severe encephalopathy; coma; life-threatening consequences	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, lactic dehydrogenase, and alkaline phosphatase.					
Hepatic hemorrhage	Mild; intervention not indicated	Symptomatic; medical intervention indicated	Transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the liver.					
Hepatic necrosis	-	-	-	Life-threatening consequences; urgent radiologic or operative intervention 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 indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the wall of the extrahepatic or intrahepatic bile duct.					

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 characterized by an increase in blood pressure in the portal venous system.					
Portal vein thrombosis	-	Intervention not indicated	Medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized 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; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Immune system disorders					
	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
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.					
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and 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 from loss of function or tissue destruction of an organ or multiple organs, arising from humoral or cellular immune responses of the individual to his own tissue constituents.					
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 characterized by nausea, headache, tachycardia, hypotension, rash, and shortness 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
Definition: A disorder characterized by a delayed-type hypersensitivity reaction to foreign proteins derived from an animal serum. It occurs approximately six to twenty-one days following the administration of the foreign antigen. Symptoms include fever, arthralgias, myalgias, skin eruptions, lymphadenopathy, chest marked discomfort and dyspnea.					
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 infestations					
	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 characterized by an infectious process involving 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
Definition: A disorder characterized by an infectious process involving the anal area and the rectum.					
Appendicitis	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by acute inflammation to the vermiform appendix caused by a pathogenic agent.					
Appendicitis perforated	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by acute inflammation to the vermiform appendix caused by a pathogenic agent with gangrenous changes resulting in the rupture of the appendiceal wall. The appendiceal wall rupture causes the release of inflammatory and bacterial contents from the appendiceal lumen into the abdominal cavity.					
Arteritis infective	-	-	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 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 characterized by an infectious process involving 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 characterized by an infectious process involving 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 characterized by an infectious process involving the bones.					
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
Definition: A disorder characterized by an infectious process involving the breast.					
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 characterized by an infectious process involving 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 characterized 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 infestations					
	Grade				
Adverse Event	1	2	3	4	5
Definition: A disorder characterized by an infectious process involving 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
Definition: A disorder characterized by an infectious process involving the uterine cervix.					
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 characterized by an infectious process involving the conjunctiva. Clinical manifestations 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 characterized by an infectious process involving 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 characterized by an infectious process involving 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
Definition: A disorder characterized by an infectious process involving the use of a medical device.					
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 characterized by an infectious process involving 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 characterized by an infectious process involving the brain tissue.					
Encephalomyelitis infection	-	-	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 brain and spinal cord tissues.					
Endocarditis infective	-	-	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 endocardial layer of the heart.					
Endophthalmitis	-	Local intervention indicated	Systemic intervention or hospitalization indicated	Blindness (20/200 or worse)	-
Definition: A disorder characterized by an infectious process involving the internal structures of the eye.					

Infections and infestations					
	Grade				
Adverse Event	1	2	3	4	5
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: A disorder characterized by an infectious process involving the small and large intestines.					
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 characterized by an infectious process involving 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 characterized by an infectious process involving 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 characterized by an infectious process involving 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 characterized by an infectious process involving 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 characterized by an infectious process involving the liver.					
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 characterized by a viral pathologic process involving 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 characterized by an infectious process involving 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 characterized by an infectious process involving a joint.					
Kidney infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the kidney.					

Infections and infestations					
	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 characterized 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 characterized by an infectious process involving 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 characterized by an infectious process involving 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 characterized by an infectious process involving the lymph nodes.					
Mediastinal infection	-	-	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 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 characterized 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 characterized by an infectious process involving 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 characterized by an infectious process involving 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
Definition: A disorder characterized by an infectious process involving the outer ear and ear canal. Contributory factors include excessive water exposure (swimmer's ear infection) and cuts in the ear canal. Symptoms include fullness, itching, swelling and marked discomfort in the ear and ear drainage.					
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 characterized by an infectious process involving 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 intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the ovary.					

Infections and infestations					
	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 characterized by an infectious process involving 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; life-threatening consequences	Death
Definition: A disorder characterized by an eruption consisting of papules (a small, raised pimple) and pustules (a small pus filled blister), typically appearing in face, scalp, and upper chest and back Unlike acne, this rash does not present with whiteheads or blackheads, and can be symptomatic, with itchy or tender lesions.					
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 characterized by an infectious process involving the soft tissues around the nail.					
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 characterized by an infectious process involving the pelvic cavity.					
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 characterized by an infectious process involving 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
Definition: A disorder characterized by an infectious process involving the orbit of the eye.					
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
Definition: A disorder characterized by an infectious process involving the peripheral nerves.					
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 characterized by an infectious process involving the peritoneum.					
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 characterized 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 characterized by an infectious process involving the vein. Clinical manifestations include erythema, marked discomfort, swelling, and induration along the course of the infected vein.					
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 characterized by an infectious process involving 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 characterized by an infectious process involving 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 characterized by a circumscribed and elevated skin lesion filled with pus.					
Rhinitis 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	-	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 characterized by an infectious process involving 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 characterized by an infectious process involving the scrotum.					
Sepsis	-	-	-	Life-threatening consequences; urgent intervention indicated	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 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 characterized by an infectious process involving 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
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	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the small intestine.					
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 characterized by an infectious process involving soft tissues.					
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				
Adverse Event	1	2	3	4	5
Definition: A disorder characterized by an infectious process involving the spleen.					
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 characterized by an infectious process involving a stoma (surgically created opening 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 characterized by an infectious process involving 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 characterized by an infectious process involving the trachea.					
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 characterized by an infectious process involving the upper respiratory tract (nose, paranasal sinuses, pharynx, larynx, 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 characterized by an infectious process involving 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 characterized by an infectious process involving the urinary tract, most commonly 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 characterized by an infectious process involving the endometrium. It may extend to the myometrium and parametrial 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 characterized by an infectious process involving 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 characterized by an infectious process involving 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 characterized by an infectious process involving the wound.					
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 indicated	Limiting instrumental ADL; operative intervention indicated	Limiting self care ADL; elective surgery indicated	-	-
Definition: A finding of damage to the ankle joint characterized by a break in the continuity of the ankle bone. Symptoms include marked discomfort, swelling and difficulty moving the affected leg and foot.					
Aortic injury	-	-	Severe symptoms; limiting self care ADL; disabling; repair or revision indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to the aorta.					
Arterial injury	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); repair or revision not indicated	Severe symptoms; limiting self care ADL; disabling; repair or revision indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to an artery.					
Biliary 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 bile due to breakdown of a biliary anastomosis (surgical connection of two separate anatomic structures).					
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 of urine due to breakdown of a bladder anastomosis (surgical connection of two separate anatomic structures).					
Bruising	Localized or in a dependent area	Generalized	-	-	-
Definition: A finding of injury of the soft tissues or bone characterized by leakage of blood into surrounding tissues.					
Burn	Minimal symptoms; intervention not indicated	Medical intervention; minimal debridement indicated	Moderate to major debridement or reconstruction indicated	Life-threatening consequences	Death
Definition: A finding of impaired integrity to the anatomic site of an adverse thermal reaction. Burns can be caused by exposure to chemicals, direct heat, electricity, flames and radiation. The extent of damage depends on the length and intensity of exposure and time until provision of treatment.					
Dermatitis radiation	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 cutaneous inflammatory reaction occurring as a result of exposure to biologically effective levels of ionizing radiation.					
Esophageal 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 due to breakdown of an esophageal anastomosis (surgical connection of two separate anatomic structures).					
Fall	Minor with no resultant injuries; intervention not indicated	Symptomatic; noninvasive intervention indicated	Hospitalization indicated	-	-
Definition: A finding of sudden movement downward, usually resulting in injury.					
Fallopian tube anastomotic leak	Asymptomatic; clinical or 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 due to breakdown of a fallopian tube anastomosis (surgical connection of two separate anatomic structures).					
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 diagnostic observations only; intervention not indicated	Symptomatic but non-displaced; immobilization indicated	Severe symptoms; displaced or open wound with bone exposure; disabling; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of traumatic injury to the bone in which the continuity of the bone is broken.					

Injury, poisoning and procedural complications					
	Grade				
Adverse Event	1	2	3	4	5
Gastric 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 due to breakdown of a gastric anastomosis (surgical connection of two separate anatomic structures).					
Gastrointestinal 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 due to breakdown of a gastrointestinal anastomosis (surgical connection of two separate anatomic structures).					
Gastrointestinal stoma necrosis	-	Superficial necrosis; intervention not indicated	Severe symptoms; hospitalization or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of a necrotic process occurring in the gastrointestinal tract stoma.					
Hip fracture	-	Hairline fracture; mild pain; limiting instrumental ADL; non-surgical intervention indicated	Severe pain; hospitalization or intervention indicated for pain control (e.g., traction); operative intervention indicated	Life-threatening consequences; symptoms associated with neurovascular compromise	-
Definition: A finding of traumatic injury to the hip in which the continuity of either the femoral head, femoral neck, intertrochanteric or subtrochanteric regions is broken.					
Injury to carotid artery	-	-	Severe symptoms; limiting self care ADL (e.g., transient cerebral ischemia); repair or revision indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the carotid artery.					
Injury to inferior vena cava	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the inferior vena cava.					
Injury to jugular vein	-	-	Symptomatic limiting self care ADL; disabling; repair or revision indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the jugular vein.					
Injury to superior vena cava	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; repair or revision not indicated	Severe symptoms; limiting self care ADL; disabling; repair or revision indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to the superior vena cava.					
Intestinal stoma 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 contents from an intestinal stoma (surgically created opening on the surface of the body).					
Intestinal stoma obstruction	-	Self-limited; intervention not indicated	Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of blockage of the normal flow of the contents of the intestinal stoma.					
Intestinal stoma 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 leakage from the intestinal stoma.					
Intraoperative arterial 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 an artery during a surgical procedure.					
Intraoperative breast 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

Injury, poisoning and procedural complications					
	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
Definition: A finding of damage to the heart during a surgical procedure.					
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
Definition: A finding of damage to the ear during a surgical procedure.					
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 surgical 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 during 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 surgical procedure.					
Intraoperative hemorrhage	-	-	Postoperative radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of uncontrolled bleeding during a surgical procedure.					
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 biliary tract during a surgical procedure.					
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 the musculoskeletal system during a surgical procedure.					
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
Definition: A finding of damage to the nervous system during a surgical procedure.					
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 procedure.					
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 procedure.					
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; disabling	Life-threatening consequences; urgent intervention indicated	Death

Injury, poisoning and procedural complications					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A finding of damage to the reproductive organs during a surgical procedure.					
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 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 procedure.					
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 the spleen during a surgical procedure.					
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 the urinary system during a surgical procedure.					
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 a vein during a surgical procedure.					
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 kidney anastomosis (surgical connection of two separate anatomic structures).					
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 due to breakdown of an anastomosis (surgical connection of two separate anatomic structures) in the large 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 due to breakdown of a pancreatic anastomosis (surgical connection of two separate anatomic structures).					
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 due to breakdown of a pharyngeal anastomosis (surgical connection of two separate anatomic structures).					
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 occurring after a surgical procedure.					
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 previously undocumented problem that occurs after a thoracic procedure.					
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 surface.					
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 displacement 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 chemotherapeutic agents, for weeks or months following radiotherapy. The inflammatory reaction is confined to the previously irradiated skin and the symptoms disappear after the removal of the pharmaceutical agent.					
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 due to breakdown of a rectal anastomosis (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.					
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 due to breakdown of an anastomosis (surgical connection of two separate anatomic structures) in the small 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 due to breakdown of a spermatic cord anastomosis (surgical connection of two separate anatomic structures).					
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 continuity of a vertebral bone is broken.					
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 (surgically created opening on the surface of the body).					
Stomal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the jejunal mucosal surface close to the anastomosis site following a gastroenterostomy procedure.					
Tracheal hemorrhage	Minimal bleeding identified on clinical or diagnostic 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 trachea.					
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
Definition: A finding of blockage of the lumen of the trachea.					

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 leakage 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
Definition: A finding of leakage due to breakdown of a ureteral anastomosis (surgical connection of two separate anatomic structures).					
Urethral 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 due to breakdown of a urethral anastomosis (surgical connection of two 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 contents from a urostomy.					
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 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 due to breakdown of a uterine anastomosis (surgical connection of two 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
Definition: A disorder characterized by a rupture in the uterine wall.					
Vaginal 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 due to breakdown of a vaginal anastomosis (surgical connection of two separate anatomic structures).					
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 due to breakdown of a vas deferens anastomosis (surgical connection of two separate anatomic structures).					
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
Definition: A finding of a previously undocumented problem related to the vascular access site.					

Injury, poisoning and procedural 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
Definition: A finding of development of a new problem at the site of an existing wound.					
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 dehiscence 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.					
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 broken.					
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	-	-
Definition: An abnormal laboratory test result in which the partial thromboplastin time is found to be greater than the control value. As a possible indicator of coagulopathy, a prolonged partial thromboplastin time (PTT) may occur in a variety of diseases and disorders, both primary and related to treatment.					
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 laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in 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 laboratory test results that indicate an increase in the level of alkaline phosphatase 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 laboratory test results that indicate an 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 laboratory test results that indicate abnormal levels of antidiuretic hormone 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 laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated 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 laboratory test results that indicate an decrease in levels of corticotrophin 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 laboratory test results that indicate abnormal levels of gonadotrophin hormone 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 laboratory test results that indicate abnormal levels of prolactin hormone 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 lung 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 which indicates increased levels of cardiac troponin I in a biological specimen.					
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 biological specimen.					
CD4 lymphocytes decreased	<LLN - 500/mm3; <LLN - 0.5 x 10e9 /L	<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 laboratory test results that indicate an decrease in levels of CD4 lymphocytes 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 laboratory test results that indicate higher than normal levels of cholesterol 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 laboratory test results that indicate an increase in levels of creatine phosphokinase 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 laboratory test results that indicate increased levels of creatinine in a biological 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 computed when the amount of blood ejected during a ventricular contraction of the heart is compared to the amount that was present prior to the contraction.					
Electrocardiogram QT corrected interval prolonged	QTc 450 - 480 ms	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 dysrhythmia characterized by an abnormally long corrected QT interval.					
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 laboratory test results that indicate an decrease in levels of fibrinogen 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 test results that indicate a relative decrease 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 laboratory test results that indicate higher than normal levels of the enzyme gamma-glutamyltransferase in the blood specimen. GGT (gamma-glutamyltransferase) catalyzes the transfer of a gamma glutamyl group from a gamma glutamyl peptide to another peptide, amino acids 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 laboratory test results that indicate abnormal levels of growth hormone in a biological specimen.					
Haptoglobin decreased	<LLN	-	-	-	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of haptoglobin 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 laboratory test results that indicate increased 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 laboratory test results that indicate an increase in the ratio of the patient's prothrombin time to a control sample 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 laboratory test results that indicate an increase in the level of lipase in a biological specimen.					
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9 /L	<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 laboratory test results that indicate a decrease in number of lymphocytes in a blood specimen.					
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	-
Definition: A finding based on laboratory test results that indicate an abnormal increase in the number of lymphocytes in the blood, effusions or bone marrow.					
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<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 laboratory test results that indicate a decrease in number of neutrophils in a blood specimen.					
Pancreatic enzymes decreased	<LLN and asymptomatic	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency	-	-
Definition: A finding based on laboratory test results that indicate an 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/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-
Definition: A finding based on laboratory 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 laboratory test results that indicate an 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 test results that indicate urine production is less relative to previous output.					
Vital capacity abnormal	90 - 75% of predicted value	<75 - 50% of predicted value; limiting instrumental ADL	<50% of predicted value; limiting self care ADL	-	-
Definition: A finding based on pulmonary function test results that indicate an abnormal vital capacity (amount of exhaled after a maximum inhalation) when compared to the predicted value.					
Weight gain	5 - <10% from baseline	10 - <20% from baseline	>=20% from baseline	-	-
Definition: A finding characterized by an increase in overall body weight; for pediatrics, greater than the baseline growth curve.					
Weight loss	5 to <10% from baseline; intervention not indicated	10 - <20% from baseline; nutritional support indicated	>=20% from baseline; tube feeding or TPN indicated	-	-
Definition: A finding characterized by a decrease in overall body weight; for pediatrics, less than the baseline growth curve.					
White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate an decrease in number of white blood cells in a blood specimen.					
Investigations - 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

Metabolism and nutrition disorders					
	Grade				
Adverse Event	1	2	3	4	5
Acidosis	pH <normal, but >=7.3	-	pH <7.3	Life-threatening consequences	Death
Definition: A disorder characterized by abnormally high acidity (high hydrogen-ion concentration) of the blood and other body tissues.					
Alcohol intolerance	-	Present	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in sensitivity to the adverse effects of alcohol, which can include nasal congestion, skin flushes, heart dysrhythmias, nausea, vomiting, indigestion and headaches.					
Alkalosis	pH >normal, but <=7.5	-	pH >7.5	Life-threatening consequences	Death
Definition: A disorder characterized by abnormally high alkalinity (low hydrogen-ion concentration) of the blood and other body tissues.					
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 characterized 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 characterized by excessive loss of water from the body. It is usually caused by severe diarrhea, vomiting or diaphoresis.					
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 characterized by an inability to properly metabolize 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; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of calcium (corrected for albumin) 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 characterized by laboratory test results that indicate an elevation in the concentration of blood sugar. It is usually an indication of diabetes mellitus or glucose intolerance.					
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 characterized by laboratory test results that indicate an elevation in the concentration of potassium in the blood; associated with kidney failure or sometimes with the use of diuretic drugs.					
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 characterized by laboratory test results that indicate an elevation in the concentration of magnesium in the blood.					
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of sodium in the blood.					
Hypertriglyceridemia	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
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of triglyceride concentration in the blood.					
Hyperuricemia	>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
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of uric acid.					
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of albumin in the blood.					

Metabolism and nutrition disorders					
	Grade				
Adverse Event	1	2	3	4	5
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized 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 characterized by laboratory test results that indicate a low concentration of calcium (corrected for albumin) in the blood.					
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<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 characterized by laboratory test results that indicate a low concentration of glucose in the blood.					
Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of potassium in the blood.					
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<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 characterized by laboratory test results that indicate a low concentration of magnesium in the blood.					
Hyponatremia	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of sodium in the blood.					
Hypophosphatemia	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<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 characterized by laboratory test results that indicate a low concentration of phosphates in the blood.					
Iron overload	-	Moderate symptoms; intervention not indicated	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by accumulation of iron in the tissues.					
Obesity	-	BMI 25 - 29.9 kg/m2	BMI 30 - 39.9 kg/m2	BMI >=40 kg/m2	-
Definition: A disorder characterized by having a high amount of body fat.					
Tumor lysis syndrome	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by metabolic abnormalities that result from a spontaneous or therapy-related cytolysis of tumor cells.					
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				
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 characterized by a necrotic process occurring in the soft tissues of the abdominal wall.					
Arthralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in a joint.					
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 characterized by inflammation involving a joint.					
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
Definition: A disorder characterized by necrotic changes in the bone tissue due to interruption of blood supply. Most often affecting the epiphysis of the long bones, the necrotic changes result in the collapse and the destruction of the bone structure.					
Back pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the back region.					
Bone pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the bones.					
Buttock pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the buttocks.					
Chest wall pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation 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 characterized 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 characterized 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 characterized by marked discomfort sensation on the lateral side of the body in the region below the ribs and above 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 characterized by a reduction in the strength of muscles in multiple anatomic sites.					
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	-	-
Definition: A disorder characterized by of stature that is smaller than normal as expected for age.					

Musculoskeletal and connective tissue disorders					
	Grade				
Adverse Event	1	2	3	4	5
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 characterized 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 characterized by excessive fluid in a joint, usually as a result of joint inflammation.					
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 characterized 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 characterized by a decrease in flexibility of a cervical spine joint.					
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 characterized 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 characterized by an abnormal increase in the curvature of the thoracic portion 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 characterized 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 characterized by a reduction in the strength of the muscles on the left side of the 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 characterized by a reduction in the strength of 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 characterized by a reduction in the strength of the muscles on the right side of the body.					
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	-	-
Definition: A disorder characterized by a reduction in the strength of the trunk muscles.					
Muscle weakness upper 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 characterized by a reduction in the strength of the upper limb muscles.					

Musculoskeletal and connective tissue disorders					
	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 characterized by of a malformation of the musculoskeletal system.					
Myalgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation originating from a muscle or group 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 characterized by inflammation involving the skeletal muscles.					
Neck pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the neck area.					
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 characterized 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 characterized 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 characterized by reduced bone mass, with a decrease in cortical thickness and in the number and size of the trabeculae of cancellous bone (but normal chemical composition), resulting in increased fracture incidence.					
Pain in extremity	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the upper or lower extremities.					
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
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the pelvis.					
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 characterized by a malformed, lateral curvature 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 characterized by a necrotic process occurring in the soft tissues of the lower extremity.					
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
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the upper extremity.					

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 characterized 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 characterized by lack of ability to open the mouth 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	Severe length discrepancy >5 cm; limiting self care ADL; disabling; operative intervention indicated	-	-
Definition: A disorder characterized by of a discrepancy between the lengths of the lower or upper extremities.					
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 benign, malignant and unspecified (incl cysts and polyps)					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Leukemia secondary to oncology chemotherapy	-	-	-	Present	Death
Definition: A disorder characterized by leukemia arising as a result of the mutagenic effect of chemotherapy agents.					
Myelodysplastic syndrome	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by insufficiently healthy hematapoietic cell production by the bone marrow.					
Treatment related secondary malignancy	-	-	Non life-threatening secondary malignancy	Acute life-threatening secondary malignancy; blast crisis in leukemia	Death
Definition: A disorder characterized by development of a malignancy most probably as a result of treatment for a previously existing malignancy.					
Tumor pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort from a neoplasm that may be pressing on a nerve, blocking blood vessels, inflamed or fractured from metastasis.					
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					
	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 characterized by involvement of the abducens nerve (sixth cranial nerve).					
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 characterized by involvement of the accessory 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 characterized by involvement of the acoustic nerve (eighth cranial nerve).					
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 characterized by an uncomfortable feeling of inner restlessness and inability to stay still; this is a side effect of some psychotropic drugs.					
Amnesia	Mild; transient memory loss	Moderate; short term memory loss; limiting instrumental ADL	Severe; long term memory loss; limiting self care ADL	-	-
Definition: A disorder characterized by systematic and extensive loss of memory.					
Aphonia	-	-	Voicelessness; unable to speak	-	-
Definition: A disorder characterized by the inability to speak. It may result from injuries to the vocal cords or may be functional (psychogenic).					
Arachnoiditis	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the arachnoid membrane and adjacent subarachnoid space.					
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 characterized by lack of coordination of muscle movements resulting in the impairment or inability to perform voluntary 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 characterized by regional paresthesia of the brachial plexus, marked discomfort and muscle weakness, and limited 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 characterized by a necrotic process occurring 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 characterized by loss of cerebrospinal fluid into 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 characterized by a conspicuous change in cognitive 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	-	-
Definition: A disorder characterized by a deterioration in the ability to concentrate.					

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 characterized by a decrease in ability to perceive and respond.					
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 characterized by a disturbing sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking.					
Dysarthria	Mild slurred speech	Moderate impairment of articulation or slurred speech	Severe impairment of articulation or slurred speech	-	-
Definition: A disorder characterized by slow and slurred speech resulting from an inability to coordinate 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 characterized by distortion of sensory perception, 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 characterized by abnormal sensual experience with the taste of foodstuffs; it can 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 characterized by impairment of verbal communication skills, often resulting from brain damage.					
Edema cerebral	-	-	-	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the brain.					
Encephalopathy	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a pathologic process involving the brain.					
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 characterized by abnormal, repetitive, involuntary muscle movements, frenzied speech and extreme restlessness.					
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 characterized by a reduction in the strength 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 characterized by involvement of the facial nerve (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 characterized by involvement of the glossopharyngeal nerve (ninth cranial nerve).					
Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in various parts of the head, not confined to the area of distribution 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 characterized by an abnormal increase of cerebrospinal fluid in the ventricles of the brain.					
Hypersomnia	Mild increased need for sleep	Moderate increased need for sleep	Severe increased need for sleep	-	-
Definition: A disorder characterized 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 diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the hypoglossal 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 characterized by bleeding from the cranium.					
Ischemia cerebrovascular	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	-	-	-
Definition: A disorder characterized by a decrease or absence of blood supply to the brain caused by obstruction (thrombosis or embolism) of an artery resulting in neurological damage.					
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 characterized by involvement of the trochlear nerve (fourth cranial nerve).					
Lethargy	Mild symptoms; reduced alertness and awareness	Moderate symptoms; limiting instrumental ADL	-	-	-
Definition: A disorder characterized by a decrease in consciousness characterized by mental and physical 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 characterized by diffuse reactive astrocytosis with multiple areas of necrotic foci without inflammation.					
Memory impairment	Mild memory impairment	Moderate memory impairment; limiting instrumental ADL	Severe memory impairment; limiting self care ADL	-	-
Definition: A disorder characterized by a deterioration in memory function.					
Meningismus	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by neck stiffness, headache, and photophobia resulting from irritation of the cerebral meninges.					
Movements involuntary	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by uncontrolled and purposeless movements.					
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 characterized by inflammation involving the spinal cord. Symptoms include weakness, paresthesia, sensory loss, marked discomfort and incontinence.					
Neuralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by intense painful sensation along a nerve or group of nerves.					
Nystagmus	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involuntary movements of the eyeballs.					
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 characterized by involvement of the oculomotor nerve (third cranial nerve).					
Olfactory nerve disorder	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the olfactory nerve (first cranial nerve).					

Nervous system disorders					
	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 characterized by functional disturbances of sensory neurons resulting in abnormal cutaneous sensations of tingling, numbness, pressure, cold, and warmth that are experienced in the absence of a stimulus.					
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 characterized by inflammation or degeneration 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 characterized by inflammation or degeneration of the peripheral sensory nerves.					
Phantom pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort related to a limb or an organ that is removed from or is not physically part of the body.					
Presyncope	-	Present (e.g., near fainting)	-	-	-
Definition: A disorder characterized by an episode of lightheadedness and dizziness which may precede an episode of syncope.					
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
Definition: A disorder characterized by dysfunction of the corticospinal (pyramidal) tracts of the spinal cord. Symptoms include an increase in the muscle tone in the lower extremities, hyperreflexia, positive Babinski and a decrease in fine motor coordination.					
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 characterized by inflammation involving a nerve root. Patients experience marked discomfort radiating along a nerve path because of spinal pressure on the connecting nerve root.					
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 characterized by paralysis of the recurrent laryngeal 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
Definition: A disorder characterized by headaches, mental status changes, visual disturbances, and seizures associated with imaging findings of posterior leukoencephalopathy. It has been observed in association with hypertensive encephalopathy, eclampsia, and immunosuppressive and cytotoxic drug treatment. It is an acute or subacute reversible condition.					
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 characterized by a sudden, involuntary skeletal muscular contractions of cerebral or brain stem origin.					
Sinus pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort in the face, between the eyes, or upper teeth 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 characterized 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 by increased involuntary muscle tone that affects the regions interfering with voluntary movement. It results in gait, movement, and speech disturbances.					
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 characterized by a sudden loss of sensory function due to an intracranial vascular event.					
Syncope	-	-	Fainting; orthostatic collapse	-	-
Definition: A disorder characterized by spontaneous loss of consciousness caused by insufficient blood supply to the brain.					

Nervous system disorders					
	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 characterized by a brief attack (less than 24 hours) of cerebral dysfunction of vascular origin, with no persistent neurological deficit.					
Tremor	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by the uncontrolled shaking movement of the whole body or individual 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 characterized by involvement of the trigeminal 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 characterized by involvement of the vagus nerve (tenth cranial nerve).					
Vasovagal reaction	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a sudden drop of the blood pressure, bradycardia, and peripheral vasodilation that may lead to loss of consciousness. It results from an increase in the stimulation of the vagus nerve.					
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

Pregnancy, puerperium and perinatal conditions					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Fetal death	-	-	-	-	Fetal loss at any gestational age
Definition: A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without 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 characterized by inhibition of fetal growth resulting 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 characterized by delivery of a viable infant before the normal end of gestation. Typically, viability is achievable between the twentieth and thirty-seventh week of gestation.					
Unintended pregnancy	-	-	Unintended pregnancy	-	-
Definition: A disorder characterized by an unexpected pregnancy at 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; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Psychiatric disorders					
	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
Definition: A disorder characterized by a state of restlessness associated with unpleasant feelings of irritability and tension.					
Anorgasmia	Inability to achieve orgasm not adversely affecting relationship	Inability to achieve orgasm adversely affecting relationship	-	-	-
Definition: A disorder characterized by an inability to achieve orgasm.					
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 characterized by apprehension of danger and dread accompanied by restlessness, tension, tachycardia, and dyspnea unattached to a clearly identifiable stimulus.					
Confusion	Mild disorientation	Moderate disorientation; limiting instrumental ADL	Severe disorientation; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a lack of clear and orderly thought and behavior.					
Delayed orgasm	Delay in achieving orgasm not adversely affecting relationship	Delay in achieving orgasm adversely affecting relationship	-	-	-
Definition: A disorder characterized by sexual dysfunction characterized by a delay in climax.					
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 characterized by the acute and sudden development of confusion, illusions, movement changes, inattentiveness, agitation, and hallucinations. Usually, it is a reversible condition.					
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 characterized by false personal beliefs held contrary to reality, despite contradictory evidence and common sense.					
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 characterized by melancholic feelings of grief or unhappiness.					
Euphoria	Mild mood elevation	Moderate mood elevation	Severe mood elevation (e.g., hypomania)	-	-
Definition: A disorder characterized by an exaggerated feeling of well-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 characterized by a false sensory perception in the absence of an external stimulus.					
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 characterized by difficulty in falling asleep and/or remaining asleep.					
Libido decreased	Decrease in sexual interest not adversely affecting relationship	Decrease in sexual interest adversely affecting relationship	-	-	-
Definition: A disorder characterized 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 characterized 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 characterized by excitement of psychotic proportions manifested by mental and physical hyperactivity, disorganization 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 disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A disorder characterized by a conspicuous change in a 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 characterized by personality change, impaired functioning, and loss of touch with reality. It may be a manifestation of schizophrenia, bipolar disorder or brain tumor.					
Restlessness	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by an inability to rest, relax or be 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 characterized by thoughts of taking one's own 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 characterized by self-inflicted harm in an attempt 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	Creatinine 2 - 3 x above baseline	Creatinine >3 x baseline or >4.0 mg/dL; hospitalization indicated	Life-threatening consequences; dialysis indicated	Death
Definition: A disorder characterized by the acute loss of renal function and is traditionally classified as pre-renal (low blood flow into kidney), renal (kidney damage) and post-renal causes (ureteral or bladder outflow obstruction).					
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 characterized by a rupture in the bladder wall.					
Bladder spasm	Intervention not indicated	Antispasmodics indicated	Hospitalization indicated	-	-
Definition: A disorder characterized by a sudden and involuntary contraction of the bladder wall.					
Chronic kidney disease	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN - 60 ml/min/1.73 m2 or proteinuria 2+ present; urine protein/creatinine >0.5	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 characterized by gradual and usually permanent loss of kidney function resulting 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 characterized by inflammation of the bladder which is not caused by an infection 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 characterized by laboratory test results that indicate blood in the urine.					
Hemoglobinuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characterized by laboratory test results that indicate the presence of free hemoglobin 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 characterized by laboratory test results that indicate the presence of excessive protein in the urine. It is predominantly 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 characterized by the formation of crystals in the 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	-	-
Definition: A disorder characterized by paroxysmal and severe flank marked discomfort radiating to the inguinal area. Often, the cause is the passage of kidney stones.					

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 characterized 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 characterized by an abnormal communication between any part of the urinary system and another organ or anatomic site.					
Urinary frequency	Present	Limiting instrumental ADL; medical management indicated	-	-	-
Definition: A disorder characterized by urination at short intervals.					
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 characterized by inability to control the flow of 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 characterized by accumulation of urine within the bladder because of the inability 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 characterized 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 characterized by a sensation of marked discomfort in the urinary tract.					
Urinary urgency	Present	Limiting instrumental ADL; medical management indicated	-	-	-
Definition: A disorder characterized by a sudden compelling urge to urinate.					
Urine discoloration	Present	-	-	-	-
Definition: A disorder characterized 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

Reproductive system and breast disorders					
	Grade				
Adverse Event	1	2	3	4	5
Azoospermia	-	-	Absence of sperm in ejaculate	-	-
Definition: A disorder characterized by laboratory test results that indicate complete absence of spermatozoa in the semen.					
Breast atrophy	Minimal asymmetry; minimal atrophy	Moderate asymmetry; moderate atrophy	Asymmetry >1/3 of breast volume; severe atrophy	-	-
Definition: A disorder characterized by underdevelopment of the breast.					
Breast pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the breast region.					
Dysmenorrhea	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by abnormally painful abdominal cramps during menses.					
Dyspareunia	Mild discomfort or pain associated with vaginal penetration; discomfort relieved with use of vaginal lubricants or estrogen	Moderate discomfort or pain associated with vaginal penetration; discomfort or pain partially relieved with use of vaginal lubricants or estrogen	Severe discomfort or pain associated with vaginal penetration; discomfort or pain unrelieved by vaginal lubricants or estrogen	-	-
Definition: A disorder characterized by painful or difficult coitus.					
Ejaculation disorder	Diminished ejaculation	Anejaculation or retrograde ejaculation	-	-	-
Definition: A disorder characterized by problems related to ejaculation. This category includes premature, delayed, retrograde and painful ejaculation.					
Erectile dysfunction	Decrease in erectile function (frequency or rigidity of erections) but intervention not indicated (e.g., medication or use of mechanical device, penile pump)	Decrease in erectile function (frequency/rigidity of erections), erectile intervention indicated, (e.g., medication or mechanical devices such as penile pump)	Decrease in erectile function (frequency/rigidity of erections) but erectile intervention not helpful (e.g., medication or mechanical devices such as penile pump); placement of a permanent penile prosthesis indicated (not previously present)	-	-
Definition: A disorder characterized by the persistent or recurrent inability to achieve or to maintain an erection during sexual activity.					
Fallopian tube obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by blockage of the normal flow of the contents in the fallopian tube.					
Fallopian tube stenosis	Asymptomatic clinical or 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 disorder characterized by a narrowing of the fallopian tube lumen.					
Female genital tract 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 characterized by an abnormal communication between a female reproductive system organ and another organ or anatomic site.					
Feminization acquired	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by the development of secondary female sex characteristics in males due to extrinsic factors.					
Genital edema	Mild 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	Lymphorrhea; gross deviation from normal anatomic contour; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the genitals.					
Gynecomastia	Asymptomatic breast enlargement	Symptomatic (e.g., pain or psychosocial impact)	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by excessive development of the breasts in males.					
Hematosalpinx	Minimal bleeding identified on imaging study or laparoscopy; 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

Reproductive system and breast disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A disorder characterized by the presence of blood in a fallopian tube.					
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 characterized by irregular cycle or duration of menses.					
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 characterized by disturbances of milk secretion. It is not necessarily related to pregnancy that is observed in females and can be observed in males.					
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 characterized by abnormally heavy vaginal bleeding 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 characterized 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 characterized 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 characterized 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 characterized by tearing or disruption of the ovarian tissue.					
Ovulation pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in one side of the abdomen between menstrual cycles, around the time of the discharge of the ovum from the ovarian follicle.					
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 characterized by a reduction in the strength of the muscles of the pelvic floor.					
Pelvic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the pelvis.					
Penile pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the penis.					
Perineal 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 area between the genital organs and the anus.					
Premature menopause	-	-	Present	-	-
Definition: A disorder characterized by ovarian failure before the age of 40. Symptoms include hot flashes, 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

Reproductive system and breast disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A disorder characterized by bleeding from the prostate gland.					
Prostatic obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by compression of the urethra secondary to enlargement of the prostate gland. This results in voiding difficulties (straining to void, slow urine stream, and incomplete emptying of the bladder).					
Prostatic 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 prostate gland.					
Scrotal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation 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 characterized 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 characterized by blockage of the normal flow of the contents of the spermatic cord.					
Testicular disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic but not interfering with urination or sexual activities; intervention not indicated; limiting instrumental ADL	Severe symptoms; interfering with urination or sexual function; limiting self care ADL; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by involvement of the testis.					
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 characterized by bleeding from the testis.					
Testicular 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 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 characterized by an abnormal communication 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 characterized 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 characterized by blockage of the uterine outlet.					
Uterine 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 uterus.					
Vaginal discharge	Mild vaginal discharge (greater than baseline for patient)	Moderate to heavy vaginal discharge; use of perineal pad or tampon indicated	-	-	-
Definition: A disorder characterized by vaginal secretions. Mucus produced by the cervical glands is discharged from the vagina naturally, especially during the childbearing years.					
Vaginal dryness	Mild vaginal dryness not interfering with sexual function	Moderate vaginal dryness interfering with sexual function or causing frequent discomfort	Severe vaginal dryness resulting in dyspareunia or severe discomfort	-	-
Definition: A disorder characterized by an uncomfortable feeling of itching and burning in the vagina.					

Reproductive system and breast 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 characterized 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 characterized 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 characterized by inflammation involving the vagina. Symptoms may include redness, edema, marked discomfort and an increase in vaginal discharge.					
Vaginal obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by blockage of vaginal canal.					
Vaginal 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 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 characterized 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 characterized by a narrowing of the vaginal canal.					
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 characterized by involuntary spasms of the pelvic floor muscles, resulting in pathologic tightness of the vaginal wall during penetration such as during sexual intercourse.					
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

Respiratory, thoracic and mediastinal 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 characterized by progressive and life-threatening pulmonary distress in the absence of an underlying pulmonary condition, usually following major trauma or surgery.					
Allergic rhinitis	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by an inflammation of the nasal mucous membranes caused by an IgE-mediated response to external allergens. The inflammation may also involve the mucous membranes of the sinuses, eyes, middle ear, and pharynx. Symptoms include sneezing, nasal congestion, rhinorrhea and itching.					
Apnea	-	-	Present; medical intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by cessation of breathing.					
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 characterized by inhalation of solids or liquids into the lungs.					
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 characterized by the collapse of part or the entire lung.					
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 characterized by an abnormal communication between the bronchus and another 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 characterized by blockage of a bronchus passage, most often by bronchial secretions 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
Definition: A disorder characterized by a narrowing of the bronchial tube.					
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 characterized by an abnormal communication between a bronchus and the pleural cavity.					
Bronchopulmonary 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 characterized by bleeding from the bronchial wall and/or lung parenchyma.					

Respiratory, thoracic and mediastinal disorders					
	Grade				
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 characterized by a sudden contraction of the smooth muscles of the bronchial wall.					
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 characterized by milky pleural effusion (abnormal collection of fluid) resulting from 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 characterized by sudden, often repetitive, spasmodic contraction of the thoracic cavity, resulting in violent release of air from the lungs and usually accompanied by a distinctive sound.					
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 characterized 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 characterized 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 characterized by repeated gulp sounds that result from an involuntary opening and closing of the glottis. This is attributed to a spasm of the diaphragm.					
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 characterized by harsh and raspy voice arising 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
Definition: A disorder characterized by a decrease in the level of oxygen in the body.					
Laryngeal 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
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the larynx.					
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 characterized 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 characterized by bleeding from the larynx.					
Laryngeal inflammation	Mild sore throat; raspy voice	Moderate sore throat; analgesics indicated	Severe throat pain; endoscopic intervention indicated	-	-
Definition: A disorder characterized by an inflammation involving the larynx.					

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 characterized by an inflammation involving the mucous membrane of the larynx.					
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 characterized by blockage of the laryngeal airway.					
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
Definition: A disorder characterized by a narrowing of the laryngeal airway.					
Laryngopharyngeal dysesthesia	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 characterized by an uncomfortable persistent sensation in the area of the laryngopharynx.					
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 characterized by paroxysmal spasmodic muscular contraction of the vocal cords.					
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 characterized by bleeding from the mediastinum.					
Nasal congestion	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Associated with bloody nasal discharge or epistaxis	-	-
Definition: A disorder characterized by obstruction of the nasal passage due to mucosal edema.					
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 characterized by an abnormal communication between the pharynx and another organ or anatomic site.					
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 characterized by bleeding from the pharynx.					
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 characterized by an inflammation involving the mucous membrane of the pharynx.					
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 characterized 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 characterized by a narrowing of the pharyngeal airway.					
Pharyngolaryngeal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation 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	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by an increase in amounts of fluid within the pleural cavity. Symptoms include shortness of breath, cough and marked chest discomfort.					
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 characterized by bleeding from the pleural cavity.					
Pleuritic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the pleura.					
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
Definition: A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma.					
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 characterized 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 characterized by excessive mucous secretion in the back of the nasal cavity or throat, causing sore throat and/or coughing.					
Productive cough	Occasional/minimal production of sputum with cough	Moderate sputum production; limiting instrumental ADL	Persistent or copious production of sputum; limiting self care ADL	-	-
Definition: A disorder characterized by expectorated secretions upon coughing.					
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 characterized by accumulation of fluid in the lung tissues that causes a disturbance 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 characterized by the replacement of the lung tissue by connective tissue, leading to progressive dyspnea, respiratory 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

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A disorder characterized by an abnormal communication between the lung and another organ 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 characterized by an increase in pressure within 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 characterized by impaired gas exchange by the respiratory system resulting in hypoxemia and a decrease in oxygenation of the tissues that may be associated with an increase in arterial levels of carbon dioxide.					
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 characterized by weight gain, dyspnea, pleural and pericardial effusions, leukocytosis and/or renal failure originally described in patients treated with all-trans retinoic acid.					
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 characterized by involvement of the paranasal 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 characterized by cessation of breathing for short periods during sleep.					
Sneezing	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized 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 characterized 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 characterized by a high pitched breathing sound due to laryngeal or upper airway 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 characterized by an abnormal communication between the trachea and another 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
Definition: A disorder characterized by an inflammation involving the mucous membrane of the trachea.					
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 characterized by a narrowing of the trachea.					

Respiratory, thoracic and mediastinal 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 characterized by a change in the sound and/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 characterized by a high-pitched, whistling sound during breathing. It results from the narrowing or obstruction of the 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 cover the hair loss but it does not require a wig or hair piece to camouflage	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; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by a decrease in density of hair compared to normal for a given individual 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 characterized by an abnormal body smell resulting from the growth of bacteria on the body.					
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 characterized by inflammation of the skin characterized by the presence of bullae which are filled with fluid.					
Dry 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 characterized 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 characterized by target lesions (a pink-red ring around a pale center).					
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 characterized by generalized inflammatory erythema and exfoliation. The inflammatory process involves > 90% of 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	-	-
Definition: A disorder characterized by shrinking of adipose tissue.					
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 characterized by the presence of excess hair growth in women in anatomic sites where growth is considered to be a secondary male characteristic and under androgen control (beard, moustache, chest, abdomen)					
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	-	-
Definition: A disorder characterized by excessive perspiration.					

Skin and subcutaneous tissue disorders					
	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 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 destructive means of hair removal to camouflage; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by hair density or length beyond the accepted limits of normal in a particular body region, for a particular age or race.					
Hypohidrosis	-	Symptomatic; limiting instrumental ADL	Increase in body temperature; limiting self care ADL	Heat stroke	Death
Definition: A disorder characterized by reduced sweating.					
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 characterized by hypertrophy of the subcutaneous adipose tissue at the site of multiple subcutaneous injections of insulin.					
Nail discoloration	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characterized by a change in the color of the nail plate.					
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 characterized by loss of all or a portion of the nail.					
Nail ridging	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characterized 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 characterized by marked discomfort sensation in the skin.					
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	-	-
Definition: A disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of the hands or the soles of the feet.					
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 characterized by swelling due to an excessive 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
Definition: A disorder characterized by an increase in sensitivity of the skin to light.					

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 characterized 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	-	-
Definition: A disorder characterized by hemorrhagic areas of the skin and mucous membrane. Newer lesions appear reddish in color. Older lesions are usually a darker purple color and eventually become a brownish-yellow 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; life-threatening consequences	Death
Definition: A disorder characterized by an eruption of papules and pustules, typically appearing in face, 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	-	-
Definition: A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbillform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and associated with pruritus.					
Scalp pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation 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 characterized by the degeneration and thinning of the epidermis and dermis.					
Skin hyperpigmentation	Hyperpigmentation covering <10% BSA; no psychosocial impact	Hyperpigmentation covering >10% BSA; associated psychosocial impact	-	-	-
Definition: A disorder characterized 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 characterized 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 characterized by an area of hardness in the skin.					
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
Definition: A disorder characterized by circumscribed, inflammatory and necrotic erosive lesion on the skin.					

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 characterized by less than 10% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.					
Telangiectasia	Telangiectasias covering <10% BSA	Telangiectasias covering >10% BSA; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by local dilatation of small vessels resulting in red discoloration of 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 characterized by greater than 30% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the 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 at age 40 - 45 years of age	Menopause occurring before age 40 years of age	-	-
Definition: A disorder characterized by the permanent cessation of menses, usually defined by 12 consecutive months of amenorrhea in 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 procedures - 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

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
Definition: A disorder characterized by leakage of intravascular fluids into the extravascular space. This syndrome is observed in patients who demonstrate a state of generalized leaky capillaries following shock syndromes, low-flow states, ischemia-reperfusion injuries, toxemias, medications, or poisoning. It can lead to generalized edema and multiple organ 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 characterized by episodic reddening of the face.					
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 characterized by a localized collection of blood, usually clotted, in an organ, space, or tissue, due to a break in the 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 characterized by an uncomfortable and temporary sensation of intense body warmth, flushing, sometimes accompanied 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 WNL; monotherapy indicated Pediatric: recurrent or persistent (>=24 hrs) BP >ULN; monotherapy indicated	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 characterized by a pathological increase in blood pressure; a repeatedly elevation in the blood pressure exceeding 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 characterized by a blood pressure that is below the normal expected for an individual 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
Definition: A disorder characterized by the loss of lymph fluid into the surrounding tissue or body cavity.					
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 characterized 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 characterized by a cystic lesion containing lymph.					
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 characterized by impaired circulation to an extremity.					
Phlebitis	-	Present	-	-	-
Definition: A disorder characterized by inflammation of the wall of a vein.					
Superficial thrombophlebitis	-	Present	-	-	-
Definition: A disorder characterized by a blood clot and inflammation involving a superficial vein of the extremities.					

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 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 characterized by occlusion of a vessel by a thrombus 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 characterized by inflammation involving the wall 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 characterized 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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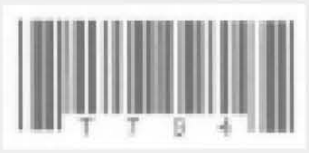

APPENDIX 2. PEMPHIGUS DISEASE AREA INDEX (PDAI)

Pemphigus Disease Area Index (PDAI)

Skin	Activity		Damage
Anatomical Locatio	Erosion/Blisters or new 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 > 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	**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 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 membrane

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**	

Total Activity Score: ☐ **Total Damage Score** ☐

APPENDIX 3. AUTOIMMUNE BULLOUS DISEASE QUALITY OF LIFE (ABQOL) QUESTIONNAIRE

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 which *blistering disease treatments* affect your quality of life.

Please choose an option from the right hand column which most closely correlates to how you felt *within the last week*.

Please time your survey in minutes and seconds – start time _____ AM/PM

1. In regards to your blistering disease, does your skin burn, sting or hurt in any way?	○ All the time ○ Sometimes ○ Occasionally ○ Not at all
2. In regards to your blistering disease, does your skin itch?	○ All the time ○ Sometimes ○ Occasionally ○ Not at all
3. Have you had to change your clothing because of your blistering disease?	○ I have to be very careful with how tight 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 ○ I have never had this problem
5. Do you have difficulty bathing or showering because of your blistering disease?	○ All the time ○ Sometimes ○ Occasionally ○ Not at all

6. In regards to your blistering disease, does your mouth have erosions which are painful?	○ All the time ○ Sometimes ○ Occasionally ○ Not at all
7. In regards to your blistering disease, do your gums bleed easily?	○ All the time ○ Sometimes ○ Occasionally ○ Not at all
8. 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

DERMATOLOGY SURVEY

This survey concerns the skin condition which has bothered you the most during the past four weeks.

Skindex29
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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	☐2	☐3	☐4	☐5
2. My skin condition affects how well I sleep	☐1	☐2	☐3	☐4	☐5
3. I worry that my skin condition may be serious	☐1	☐2	☐3	☐4	☐5
4. My skin condition makes it hard to work or do hobbies	☐1	☐2	☐3	☐4	☐5
5. My skin condition affects my social life	☐1	☐2	☐3	☐4	☐5
6. My skin condition makes me feel depressed	☐1	☐2	☐3	☐4	☐5
7. My skin condition burns or stings	☐1	☐2	☐3	☐4	☐5
8. I tend to stay at home because of my skin condition	☐1	☐2	☐3	☐4	☐5
9. I worry about getting scars from my skin condition	☐1	☐2	☐3	☐4	☐5
10. My skin itches	☐1	☐2	☐3	☐4	☐5
11. My skin condition affects how close I can be with those I love	☐1	☐2	☐3	☐4	☐5
12. I am ashamed of my skin condition	☐1	☐2	☐3	☐4	☐5
13. I worry that my skin condition may get worse	☐1	☐2	☐3	☐4	☐5
14. I tend to do things by myself because of my skin condition	☐1	☐2	☐3	☐4	☐5
15. I am angry about my skin condition	☐1	☐2	☐3	☐4	☐5
16. Water bothers my skin condition (bathing, washing hands)	☐1	☐2	☐3	☐4	☐5
17. My skin condition makes showing affection difficult	☐1	☐2	☐3	☐4	☐5
18. I worry about side-effects from skin medications / treatments	☐1	☐2	☐3	☐4	☐5
19. My skin is irritated	☐1	☐2	☐3	☐4	☐5
20. My skin condition affects my interactions with others	☐1	☐2	☐3	☐4	☐5

Please turn to next page

Skindex29

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	☐2	☐3	☐4	☐5
22. My skin condition is a problem for the people I love . . .	☐1	☐2	☐3	☐4	☐5
23. I am frustrated by my skin condition	☐1	☐2	☐3	☐4	☐5
24. My skin is sensitive	☐1	☐2	☐3	☐4	☐5
25. My skin condition affects my desire to be with people . .	☐1	☐2	☐3	☐4	☐5
26. I am humiliated by my skin condition	☐1	☐2	☐3	☐4	☐5
27. My skin condition bleeds	☐1	☐2	☐3	☐4	☐5
28. I am annoyed by my skin condition	☐1	☐2	☐3	☐4	☐5
29. My skin condition interferes with my sex life	☐1	☐2	☐3	☐4	☐5
30. My skin condition makes me tired	☐1	☐2	☐3	☐4	☐5

APPENDIX 5. COHORT 2 ALTERNATE SCHEDULE OF EVENTS TABLE

Table 10. Study Assessments for Cohort 2 (Alternate Weekly Dosing Option)

	Screening	Loading			Maintenance										Follow-Up		
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	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
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[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

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.

l. **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.

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
Amendment 1.0: 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

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. • The secondary objectives were reordered to reflect their importance.
Section 4, Study Drug	Description of SYNT001 • 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 Design	The number of study sites was increased from 10 to 20. 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 up to 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 Rules	Subject Withdrawal • 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, Evaluation of Safety	No substantial changes were made to this section; only updates to abbreviations and minor corrections for consistency. Warnings and Precautions • Allowed vaccinations were updated to 28 days after the final dose of study drug rather than discretion of investigator.
Section 11, Statistical Considerations	"Data" was updated to "analysis" in headings. Details of 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. 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.