A Phase 1b/2, Multicenter, Open-Label, Safety, and Dose-Finding Study of SYNT001 in Subjects with Pemphigus (Vulgaris or Foliaceus)

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9. DOCUMENTATION OF STATISTICAL METHODS

- Statistical Analysis Plan Version 1.0, 25 March 2019

STATISTICAL ANALYSIS PLAN

PROTOCOL SYNT001-003

A Phase 1b/2, Multicenter, Open-Label, Safety, and Dose-Finding Study of SYNT001 in Subjects with Pemphigus (Vulgaris or Foliaceus)

Investigational Product:	SYNT001
Protocol Number:	SYNT001-103
Development Phase:	Phase 1b/2
Sponsor:	Alexion Pharmaceuticals Inc. 121 Seaport Blvd Boston, MA 02210

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SIGNATURE PAGE

STUDY TITLE: A Phase 1b/2, Multicenter, Open-Label, Safety, and Dose-Finding Study of SYNT001 in Subjects with Pemphigus (Vulgaris or Foliaceus)

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We, the undersigned, have reviewed and approved this statistical analysis plan.

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Document History

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ABQoL	Autoimmune bullous diseases quality of life
AE	Adverse event
AECA	Anti-epithelial cell antibody
ATC	Anatomical therapeutic chemical
AUC	Area under curve
BLQ	Below the limit of quantification
BMI	Body mass index
C3	Complement component 3
CIC	Circulating Immune Complexes
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DEC	Dose Escalation Committee
DLT	Dose-limiting toxicities
ECG	Electrocardiogram
FCGR2A	Fc gamma R2A receptor
GM	Geometric mean
HR-QoL	Health-related quality of life
IGA	Immunoglobulin A
IGG	Immunoglobulin G
IGM	Immunoglobulin M
IV	Intravenous
MED	Minimum Effective Dose
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
PD	Pharmacodynamic
PDAI	Pemphigus Disease Area Index
PE	Physical Exam
PK	Pharmacokinetics
QTc	Corrected QT interval
QTcF	Corrected QT interval Fridericia's formula
RNA	Ribonucleic acid
SAE	Serious adverse event

SAP	Statistical analysis plan
SD	Standard deviation
SNP	Single nucleotide polymorphisms
SOC	System Organ Class
TEAE	Treatment-emergent adverse event

1. INTRODUCTION

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.

Results obtained from the analysis outlined in this document will become the basis for the final Clinical Study Report (CSR) for this protocol. This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objective and Endpoint

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 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)	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)

2.2 Secondary Objective and Endpoint

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

Secondary Objectives	Secondary Endpoints
To determine the pharmacokinetics (PK) of SYNT001 following IV infusions at different dose levels and dosing regimen	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

2.3 Exploratory Objective and Endpoint

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

Exploratory Objectives	Exploratory Endpoints
	• 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 regimen	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 time points (skin biopsies optional) (Cohort 1 only)

3. STUDY OVERVIEW

3.1 Overall Study Design and Treatment Assignment

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.

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 Protocol Section 9.5 and the DEC Charter.

An overview of the study cohorts is provided in Table 1.

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	NA
2[b]	Up to 12	Loading: 30 mg/kg[c] Maintenance: 10 mg/kg[c]	3[c] 5[c]	Weekly[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 Protocol APPENDIX 5 for the corresponding visit schedule.

The duration of subject participation for each cohort is as follows:

				Maximum Total	
Cohort	**Screening**	**Treatment**	**Follow-up**	**Days**	**Weeks**
1	≤14 days	28 days	84 days	126 days	18 weeks
2	≤14 days	84 days	56 days	154 days	22 weeks

Subjects will be enrolled at staggered intervals to facilitate adequate safety evaluation before dosing of subsequent subjects.

Refer to Table 2 and Table 3 for detail study assessments and Table 4 for Timing Windows for PK/PD Sampling, ECG, and Vital Sign Measurements.

3.1.1 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.

3.1.2 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.

3.1.3 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. All clinically significant findings at screening and Day 0 (pre-dose) will be recorded as medical history. All clinically significant findings after the first dose will be reported as adverse events.

3.1.4 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 4 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.

3.1.5 Clinical Laboratory Measurements

Laboratory testing (hematology, urinalysis, serum chemistry, virology, serology, pregnancy tests, PD, PK, and ADA) will be performed using established methods by a central laboratory.

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.

3.1.6 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.

3.1.7 Virology

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

3.1.8 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.

3.1.9 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 maximum serum concentration of SYNT001 and the associated T_{max}. Specific collection times are detailed in Table 4.

3.1.10 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 Table 5.

Samples for each type of PD will be collected according to the schedule shown in Table 5.

3.1.11 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.

3.1.12 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 4 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.

3.1.13 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).

3.1.14 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.

3.1.15 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.

3.1.16 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). 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).

3.1.17 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.

3.1.18 Prior and Concomitant Medications

All non-pemphigus treatments a subject receives within 14 days prior to enrollment (Day 0) through the last study visit will be collected. All immunosuppressants, corticosteroids or blood transfusions a subject has received in 3 months (90 days) prior to enrollment and all rituxan cycles a subject has received in 5 years prior to enrollment will also be documented.

3.1.19 Skin Biopsy

In Cohort 1, optional skin biopsy samples from lesional or non-lesional skin will be collected to analyze SYNT001 levels.

4. STATISTICAL METHODOLOGY

All descriptive and inferential statistical analyses will be performed using Statistical Analysis System (SAS®) software Version 9.4 or higher.

Phoenix WinNonlin Version 6.4 or higher will be used in the determination of the PK terminal phase and the calculation of PK parameters. PK parameters will be calculated via SAS and verified with the Phoenix WinNonlin results.

Missing data will not be imputed unless otherwise stated. All clinical data captured will be provided in data listings.

4.1 General Design

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 and dosing regimen (cohort), and in total. 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.

4.2 Study Populations

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

- The **Safety population** will consist of all subjects who received at least one dose of study drug.
- The **PD population** will consist of all subjects who received at least one dose of study drug and have post-dose PD data available.
- The **PK population** will consist of all subjects who received 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.

4.3 Subject Disposition

Counts and percentage of subjects who are in each study population (Safety, PK and PD populations), who complete the study, and who withdraw early from the study will be presented by cohort and in total. The primary reasons for early withdrawals will also be tabulated.

Subject disposition, inclusion / exclusion criteria and comments will be listed.

A listing of all screen failures (i.e., subjects who were screened but not enrolled) will be presented along with reasons for screen failure.

4.4 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively by cohort and in total for the Safety population and repeated for PK and PD populations if they are different from the Safety population.

Demographic and baseline characteristics include, but are not limited to, age at informed consent, gender, race, ethnicity, body weight, body mass index (BMI), age at diagnosis of

pemphigus, pemphigus disease duration at Day 0, type of pemphigus, type of tissue-based test positive for pemphigus, tissue-based test positive for pemphigus duration at Day 0, current exacerbation duration at Day 0.

Continuous variables (e.g., age, weight, and BMI) will be summarized by descriptive statistics. Categorical variables (e.g., gender, race, and ethnicity) will be summarized by the number and percentage of patients in corresponding categories.

Baseline is defined as the Day 0 (pre-dose) measurement. If missing, the last measurement prior to the first study drug administration will be used as the baseline value.

Medical/surgical history will be will be coded using the Medical Dictionary for Regulatory Activities (MedDRA 19.1) and summarized for the number and percentage for each System Organ Class (SOC) and preferred term by cohort and in total for the Safety population.

A summary table for categories of protocol deviations will be produced for major protocol deviations. Protocol deviations will also be listed for the Safety population.

4.5 Prior and Concomitant Medications

All medications administered during the study will be listed and coded using the most current version of WHO Drug Dictionary (WHO Drug Sept 2016E B2).

For prior or concomitant medications, incomplete (i.e., partially missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a subject, impute the start date first. See Appendix B for details on imputation rules.

A listing of all prior and concomitant medications including the reported term, preferred term, and anatomical therapeutic chemical (ATC) class, start and stop dates, and other relevant data will be provided.

The number and percentage of patients taking, prior medications, concomitant medications, and medication for potential infusion-related reactions (IRRs) will be summarized by cohort, ATC class, and preferred term. Concomitant medications include all medications taken on or after the first dose of the study drug. Prior medications include all medications taken before the first dose of study drug.

4.6 Study Medication Administration

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.

Dose administered (mg/kg), percentage of total dose administered (%), total administration time (minutes), volume administered (mL) and number of vials used will be summarized at each scheduled visits by cohort.

Percentage of total dose administered (%) = total dose administered / planned total dose * 100%.

Study medication administration data will be listed.

4.7 Safety Analyses

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. Baseline for safety parameters is defined as Day 0 (pre-dose) measurement. If missing, the last measurement prior to the first study drug administration will be used as the baseline value.

4.7.1 Adverse Events

Adverse events data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA 19.1). Adverse events will be graded using the NCI CTCAE, Version 4.03.

A treatment-emergent adverse event (TEAE) is defined as any AE that starts on or after the first dose of study drug or occurs prior to the first dose and worsens in severity on or after the first dose of study drug, during the treatment period and follow-up period.

For AEs with partial start dates, non-missing date parts will be used to determine if the AE is treatment-emergent or not. If a determination cannot be made using the non-missing date parts as to when the AE occurred relative to study drug administration, e.g. AE start year and month are the same as the year and month of the first dose of investigational product, then the AE will be classified as treatment-emergent. See Appendix B for details on imputation rules.

An overview of TEAEs will be provided. The overview will summarize the subject incidence of the following information:

- Any TEAEs
- Worst NCI CTCAE grade of TEAEs
- Drug-related TEAEs
- Worst NCI CTCAE grade of drug-related TEAEs
- Any study drug-related Grade 3 or greater TEAEs
- TE-SAEs
- Drug-related TE-SAEs
- TEAE leading to discontinuation of study drug
- Drug-related TEAE leading to discontinuation of study drug
- TEAE leading to study drug interruption
- Drug-related TEAE leading to study drug interruption
- TEAE leading to study drug dose reduction
- Drug-related TEAE leading to study drug dose reduction
- Death

TEAEs will also be summarized using SOC, preferred term and severity grade based on NCI CTCAE (Version 4.03). Drug-related TEAEs will be summarized by the same manner.

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.

TEAEs, SAEs, and TEAEs leading to discontinuation of study drug, dose reduction or interruption will be listed. Duration of AEs will be determined and included in listings, along with action taken and outcome.

4.7.2 Clinical Laboratory Tests

Laboratory results, percentage change and absolute change from baseline will be summarized by cohort, visit and time point using descriptive statistics. Incidence of laboratory abnormalities and laboratory NCI CTCAE (Version 4.03) will be summarized. Shift tables of CTCAE Grade for chemistry parameters (Normal, Grade 1, Grade 2, Grade 3, Grade 4, Grade 3/4, Total, Missing) from baseline to each post-baseline time point showing number and percentage of subjects with movement between categories will be presented. The worst on-study grade after the first study drug administration will be summarized.

Baseline is defined as the Day 0 (pre-dose) measurement. If the baseline measurement is missing, the last measurement prior to the first study drug administration.

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.

4.7.3 Physical Examination, Vital Signs, and Electrocardiogram Findings

The number and percentage of subjects with normal, abnormal and clinical significant , abnormal but not clinically significant physical exam findings will be summarized by visit and dose.

Vital sign measurements and change from baseline will be summarized at each scheduled time point by cohort using descriptive statistics. Baseline is defined as the Day 0 (pre-dose) measurement. If the baseline measurement is missing, the last measurement prior to the first study drug administration.

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 not clinically significant, abnormal clinically significant) from baseline to each post-baseline time point showing number and percentage of subjects with movement between categories will be presented by treatment group. The worst overall interpretation at each visit from the three triplicate readings are summarized.

The number and percentage of subjects with elevated QTcF during the post baseline period will be presented for the following categories: QTcF worsening to >450 msec, >480 msec, and >500 msec from baseline, and increase in QTcF from baseline >30 msec and >60 msec.

Actual sampling times that are outside the scheduled sampling times window described in Table 5 will be excluded from summary statistics.

4.8 Dose Selection Analyses

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. The number and proportion of patients that achieve the following criteria will be summarized (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).

4.9 Analysis of Secondary Endpoints

4.9.1 Pharmacokinetic Analysis

PK results for SYNT001 will be summarized by cohort, 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.

PK concentrations will be summarized descriptively at each nominal time point by cohort using n, mean, SD, percent coefficient of variation (CV%), standard error, median, minimum, maximum, geometric mean, geometric CV%.

Mean concentrations (±SD) of SYNT001 will be plotted on a linear and semi-logarithmic scale against nominal time points, by cohort. Individual concentration for each subject will be plotted using original scale and semi-log scale.

Study drug concentrations will be used to calculate the following PK parameters, if feasible:

Parameters	Description
C_{max}	Maximum observed plasma concentration observed directly from data
T_{max}	Time to reach maximum observed concentration directly from data
λ_z	Apparent first-order terminal elimination rate constant calculated by linear regression of the terminal linear portion of the log concentration vs. time curve
$t_{½}$	Terminal elimination half-life, calculated as $\ln(2)/ \lambda_z$
AUC_{0-24}	AUC from time zero to 24 hours post-dose administration
$AUC_{0-\infty}$	AUC from time zero to infinity time (as $AUC_{0-t} + C_{last}/ \lambda_z$, where C_{last} is the last quantifiable concentration)

Actual sampling time will be used for PK calculations. Actual sampling times that are outside the scheduled sampling times window described in Table 4 will be excluded from summary statistics of PK concentrations but will still be used in the calculations of PK parameters.

The Linear Up Log Down method will be used in the computation of AUCs. The PK parameters λ_z and $t_{1/2}$ will not be presented for subjects who do not exhibit a terminal elimination phase in their concentration-time profiles.

The constant λ_z will not be assigned if one of the following happens:

1. T_{max} is or is equal to one of the 3 last data points,
2. The adjusted regression coefficient is less than 0.8,
3. The percent of $AUC_{0-\infty}$ extrapolated exceeds 20%,
4. The estimated elimination rate indicates a positive slope, or
5. The terminal elimination phase is not linear (as appears in a semi-logarithmic scale) based on visual inspection.

In cases where the constant λ_z is not assigned, the values of associated parameters (e.g., $t_{1/2}$ and $AUC_{0-\infty}$) will not be calculated.

4.9.2 Pharmacodynamic/ Disease Activity Analysis

PD samples will be collected for analyses throughout the study. Samples for each type of PD will be collected according to the schedule shown in Table 5.

PD and disease activity markers will include but not limited to following information:

- Serum levels of total IgG,
- IgG subtypes (IgG1-4),
- Immunoglobulin A (IgA),
- Immunoglobulin M (IgM),
- Albumin,
- CIC
- Anti-Dsg 1 and 3 antibodies

All PD/disease activity data will be summarized by cohort and visit. Descriptive statistics of PD will include mean, SD, median, minimum, and maximum. Mean (±SD) of values and percentage change and absolute change from baseline will also be plotted.

4.9.3 Immunogenicity Analysis

Immunogenicity results including anti-SYNT001 antibody, anti-SYNT001 neutralizing antibodies and anti-SYNT001 antibodies titer available at the time of the database lock will be summarized by cohort, visit and time point. Descriptive statistics will include mean, SD, CV, median, minimum, and maximum.

4.9.4 PDAI data

PDAI skin activity score (0-120), mucous membrane activity score (0-120), scalp activity score (0-10), skin damage score (0-12), scalp damage score (0-1), total activity score (0-250), and total damage score (0-13) will be summarized by cohort and visit. Higher score indicates higher impact of skin disease. Descriptive statistics will include absolute change from baseline, and percentage change from baseline.

PDAI total activity score ranges from 0 to 250. The number and percentage of subject will be summarized by disease severity category based on PDAI total activity score, such as mild (0-8), moderate (9-24), and severe (≥25).

4.10 Analysis of Exploratory Endpoints

4.10.1 Exploratory Pharmacodynamic/ Activity Analysis

Exploratory PD and disease activity markers will include:

- Complement component 3
- AECA
- FCGR2A
- RNAseq
- Immunophenotyping
- Urine IgG levels to explore SYNT001 distribution and elimination (Cohort 1 only)
- Exploratory Pemphigus Immune Response Biomarkers

All exploratory PD/disease activity data will be summarized by cohort and visit. Descriptive statistics will include mean, SD, median, minimum, and maximum. Mean (±SD) of values and percentage change and absolute change from baseline will also be plotted.

4.10.2 Corticosteroid Use

The number and percent of subjects who use corticosteroid will be summarized by cohort and visit.

4.10.3 Health-Related Quality of Life Data

For Cohort 2, Autoimmune Bullous Disease Quality of Life (ABQOL) questionnaire total score will be calculated and summarized by visit.

SKINDEX-29 is a three-dimensional, dermatology-specific HRQL questionnaire. Twenty-nine items are combined to form three domains: symptoms, emotions, and functioning. The domain scores and an overall score are expressed on a 100-point scale, with higher scores indicating lower levels of quality of life.

Domains/Scales	Number of Items	Cluster of Items	Item reversion	Direction of Domains
Emotions	10	3; 6; 9; 12; 13; 15; 21; 23; 26; 28	No	Higher score = higher impact of skin disease
Symptoms	7	1; 7; 10; 16; 19; 24; 27		
Functioning	12	2; 4; 5; 8; 11; 14; 17; 20; 22; 25; 29; 30		

Note: Item 18 is a single item, not included in scoring.

All responses are transformed to a linear scale of 100. Transformed item scores: never = 0, rarely = 25, sometimes = 50, often = 75, and all the time = 100. A scale score is the mean of a patient's responses to the items in a given scale. If responses to more than 25% of items are missing overall, the questionnaire is eliminated. If any scale has more than 25% of the responses missing, the scale is missing. Scale scores are the average of non-missing items in a given scale. An item with multiple answers is considered missing.

For Cohort 2, three domain scores and the overall score from SKINDEX-29 will be summarized by visit.

4.10.4 Photography

The quantitative photography data will not be part of the database. Only visit and date of collection will be listed in data listing. No summary table will be presented.

4.10.5 Skin Biopsy

The quantitative skin biopsy data will not be part of the database. Only visit, date of collection and type of skin will be listed in data listing. No summary table will be presented.

5. SAMPLE SIZE DETERMINATION

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.

6. PROGRAMMING SPECIFICATIONS

The programming specifications, including the mock-up validity listings, analysis tables, figures, and data listings, as well as the derived database specifications, will be prepared in stand-alone documents. The programming specification documents will be finalized prior to database lock.

7. INTERIM ANALYSIS

No interim analysis is planned.

8. APPENDICES

Appendix A: Study Assessments and Timing Window

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 Protocol 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 Protocol 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 Protocol 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 Protocol 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 Protocol 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 Protocol 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 Protocol Section 7.5.5 for additional information.
l. Exploratory pharmacodynamic samples (C3 and AECA): Collected pre-dose when collected on dosing days. See Protocol 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 Protocol 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 Protocol 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 Protocol 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 Protocol 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 Protocol Section 7.5.4 for additional information.
j. Immunogenicity: Samples will be collected pre-dose when collected on dosing days. See Protocol 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 Protocol 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 Protocol Section 7.5.5 for additional information.
m. Exploratory pharmacodynamic samples (C3 and AECA): Collected pre-dose when collected on dosing days. See Protocol 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.

Table 4. 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 hour 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

Abbreviations: ECG = electrocardiogram; N/A = not applicable; PD = pharmacodynamics; PK = pharmacokinetic.
a. Vital signs to include blood pressure, pulse rate, respiratory rate, oral temperature, and pulse oximetry.

Table 5. 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 Protocol APPENDIX 5 for the corresponding visit schedule.
b Urine IgG collected in Cohort 1 only.

Appendix B: Imputation Rules for Missing Dates

Imputation Rules for Missing Prior/Concomitant Medication Dates

Imputation rules for missing or partial medication start/stop dates are defined below:

1. Missing or partial medication start date:
    - If only DAY is missing, use the first day of the month.
    - If DAY and Month are both missing, use the first day of the year.
    - If DAY, Month and Year are all missing, use a date before the first dose date (in practical, use Jan. 01, 2000 to impute).
2. Missing or partial medication stop date:
    - If only DAY is missing, use the last day of the month.
    - If DAY and Month are both missing, use the last day of the year.
    - If DAY, Month and year are all missing, assign 'continuing' status to stop date (in practical, use Dec. 31, 2050 to impute).

Imputation rules for missing or partial AE start date are defined below:

If only Day of AE start date is missing:

If the AE start year and month are the same as that for the first dose date, then:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start day as the day of first dose date; otherwise, impute the AE start day as 1.
- Otherwise, impute the AE start day as 1.

Compare the imputed AE start date with Treatment-Emergent period to determine whether the AE is pretreatment AE, TEAE or post-treatment AE.

If Day and Month of AE start date are missing:

If AE start year = first dose year, then:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start Month and Day as the Month and Day of first dose date; otherwise, impute the AE start Month as January and the Day as 1.
- Otherwise, impute the AE start MONTH as January and the DAY as 1.

Compare the imputed AE start date with Treatment-Emergent period to determine whether the AE is pretreatment AE, TEAE or post-treatment AE.

If Year of AE start date is missing:

If the year of AE start is missing or AE start date is completely missing then query site with no imputation. Also compare the full (or partial) AE end date to the first dose date. If the AE end date is before the first dose date then the AE should be considered as a pretreatment AE. Otherwise, the AE will be considered as TEAE.