A Phase 1b/2, Multicenter, Open-Label, Safety, Tolerability, and Activity Study of SYNT001 in Subjects with Warm Autoimmune Hemolytic Anemia (WAIHA)

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STATISTICAL ANALYSIS PLAN

PROTOCOL SYNT001-102

A Phase 1b/2, Multicenter, Open-Label, Safety, Tolerability, and Activity Study of SYNT001 in Subjects with Warm Autoimmune Hemolytic Anemia (WAIHA)

Investigational Product:	SYNT001
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Sponsor:	Alexion Pharmaceuticals Inc. 121 Seaport Blvd Boston, MA 02210

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STUDY TITLE: A Phase 1b/2, Multicenter, Open-Label, Safety, Tolerability, and Activity Study of SYNT001 in Subjects with Warm Autoimmune Hemolytic Anemia (WAIHA)

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Document History

Version	Date	Comments
1.0	April 09, 2019	Original version

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA	anti-drug antibodies
AE	adverse event
ANA	antinuclear antibody
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
BLQ	below the limit of quantification
BMI	body mass index
C3	complement component 3
CIC	circulating immune complexes
C_{max}	maximum observed plasma concentration observed directly from data
C_{min}	minimum observed plasma concentration observed directly from data
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV%	percent coefficient of variation
dsDNA	double-stranded deoxyribonucleic acid
ECG	electrocardiograms
ELISA	C1q-based binding assay
FCGR2A	Fc gamma R2A receptor
HIV	human immunodeficiency virus
IgA	immunoglobulin A
IgG	Immunoglobulin G
IgG1-4	IgG subtypes
IgM	immunoglobulin M
IRR	infusion-related reaction
IV	intravenous
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NK	natural killer
PD	pharmacodynamics
PE	physical examinations
PK	pharmacokinetics
QTcF	corrected QT interval using Fridericia's formula

RBC	red blood cells
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System
SD	standard deviation
SNP	single nucleotide polymorphisms
SOC	system organ class
TEAE	treatment-emergent adverse event
$t_{½}$	terminal elimination half-life
T_{max}	observed time to reach peak plasma concentration
T_{min}	time to reach minimum observed concentration directly from data
VZV	Varicella-Zoster virus
WAIHA	warm autoimmune hemolytic anemia
WHO	World Health Organization
λ_z	apparent first-order terminal elimination rate constant

1. INTRODUCTION

This study is being conducted to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity, and effects of intravenous (IV) SYNT001 in subjects with warm autoimmune hemolytic anemia (WAIHA).

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

2.1.1 Primary Objective and Endpoint

Primary Objectives	Primary Endpoints
Safety: To evaluate the safety and tolerability of IV infusions of SYNT001 at different dose levels and dosing regimens in subjects with WAIHA	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

2.1.2 Secondary Objectives and Endpoints

Secondary Objectives	Secondary Endpoints
To evaluate the efficacy of doses of SYNT001 at different dose levels and dosing regimens on 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 time point
To determine the 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

Secondary Objectives	Secondary Endpoints
	1); maximum serum concentration determined directly from the maximum serum concentration and corresponding T_{max} (Cohort 2) summarized by dose, dosing regimen and time point
To assess the efficacy of doses of SYNT001 at different dose levels and dosing regimens on disease markers	The assessment of WAIHA disease activity by absolute changes in the disease activity markers of hematocrit, hemoglobin, platelet count, reticulocyte count, lactate dehydrogenase (LDH), haptoglobin, and total and indirect bilirubin will be summarized by dose, dosing regimen and time point The direct Coombs test result (positive or negative) will be summarized by dose, dosing regimen and time point
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 and time point

2.1.3 Exploratory Objectives and Endpoints

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 time point, as determined by: • D-dimer • Antiphospholipid antibodies (lupus anticoagulant, anti-cardiolipin antibody, anti-beta-2-GP1 antibody) • Antinuclear antibody titer • Anti-dsDNA antibody titer • Quantitative Coombs assay • Cold agglutinins (titer and thermal amplitude) • Fc gamma R2A receptor (FCGR2A) single nucleotide polymorphisms (SNP) by genotyping • Complement component 3 levels by

Exploratory Objectives	Exploratory Endpoints
	nephelometry • 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
To characterize blood transfusions during the study	The number of units of packed red blood cells received by subjects will be summarized by dose and dosing regimen
To determine the impact of different SYNT001 dose levels and dosing regimens on the subject's use of corticosteroids to treat their WAIHA	The evaluation of corticosteroid use during the study will be summarized by dose, dosing regimen and time point

3. STUDY OVERVIEW

3.1 Overview of Study Design

This is a multicenter, open-label study to assess the safety, tolerability, efficacy, PK, PD, and immunogenicity of SYNT001 IV administered to subjects with WAIHA.

Up to 8 subjects with a diagnosis of WAIHA will receive SYNT001 10 mg/kg weekly x 5 doses (Cohort 1). Up to 12 subjects with a diagnosis of WAIHA will receive SYNT001 (10, 20 or 30 mg/kg) weekly x 3 doses (Loading), followed by SYNT001 (10, 20 or 30 mg/kg) every other week x 5 doses (Maintenance) or SYNT001 (10, 20 or 30 mg/kg) weekly x 10 doses (alternative weekly maintenance schedule) (Cohort 2). An overview of the study cohorts is provided in Table 1.

Table 1. Cohort Overview

Cohort	No. of subjects	SYNT001 Dose	No. of Doses	Frequency of Doses
1	Up to 8	10 mg/kg	5	Weekly
2	Up to 12	Loading: 10, 20 or 30 mg/kg Maintenance: 10, 20 or 30 mg/kg	3 5	Weekly Every other week
2 Alternative weekly schedule	Up to 12	Loading: 10, 20 or 30 mg/kg Maintenance: 10, 20 or 30 mg/kg	3 10	Weekly Weekly

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 Appendix Table 2. For Cohort 2 details, see Appendix Table 3. An alternative weekly maintenance schedule of assessment for Cohort 2 is presented in Appendix Table 4.

3.2 Study Assessments

3.2.1 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.

3.2.2 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, transfusions, concomitant treatments, and relevant clinical response to past disease specific treatments including duration and dosing of such treatments.

3.2.3 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.

3.2.4 Karnofsky Performance Scale

A Karnofsky performance scale evaluation will be conducted at screening. Subjects who score less than or equal to 50 are excluded from the study.

3.2.5 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.

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.

3.2.6 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. ECGs are to be performed in triplicate at least 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.

3.2.7 Clinical Laboratory Measurements

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

Abnormalities in clinical safety 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.

3.2.8 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.

3.2.9 Virology

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

3.2.10 Serum Tetanus Antibody and Varicella-Zoster Virus Antibody Testing

Samples for serum tetanus antibody and Varicella-Zoster virus antibody testing are to be collected.

3.2.11 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 maximum serum concentration of SYNT001 and the associated T_{max}. Specific collection times are detailed in Table 5.

3.2.12 Pharmacodynamic Sampling

PD samples will be collected for analyses throughout the study. Measurements for PD biomarkers (albumin levels, hematocrit, hemoglobin, platelet count, reticulocyte count, LDH, and total and indirect bilirubin) 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 6.

3.2.13 Immunogenicity Testing

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 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, a titer will be determined and there will be testing for neutralizing antibodies using a validated cell based assay.

3.2.14 Circulating Immune Complexes

Patients with autoimmune diseases such as WAIHA frequently have elevated levels of CICs as part of their autoimmune disease process. In these patients the degree of elevation may correlate with disease activity. In the SYNT001 phase 1a single dose escalation healthy volunteer study, almost all baseline CIC results were within the normal range. Treatment with a single IV dose of SYNT001 resulted in a dose-dependent decrease of up to 50% in CICs. CICs are most frequently assessed using either a C1q-based binding assay (ELISA), or less frequently by binding to Raji Cells via their complement receptor (Flow Cytometry).

3.2.15 Direct Antiglobulin (Coombs) Test

WAIHA is caused by autoantibodies (usually IgG) that bind to RBC antigens. This results to the activation of the complement system and deposition of complement protein C3 on the RBCs. Red blood cells coated with IgG with or without complement disposition are removed from the circulation by the reticuloendothelial system in the spleen and liver leading to anemia via a process known as extravascular hemolysis. The direct antiglobulin, or Coombs, test is used to determine whether a patient's RBCs are coated with IgG and/or complement proteins. Anti-IgG and anti-C3 antisera are added to a patient's red cells, and if IgG or C3 are present the RBCs clump or agglutinate, which is detected visually.

3.2.16 Quantitative Coombs Assay

Subject and control RBC-bound IgG, IgM and C3 will be measured by flow cytometry. RBCs coated with serial dilutions of monoclonal anti-Rh(D) IgG and IgM serve as positive controls. Quantum™ MESF (Molecules of Equivalent Soluble Fluorochrome) microsphere beads

coated with known numbers of fluorescent dye molecules are used as internal validation markers prior to analysis. Dynabeads® Protein G are used to quantify binding of mouse anti-human IgG, IgM and C3 antibodies. Binding of IgG is expressed as the geometric mean of the fluorescence intensity.

3.2.17 Study Drug Administration

Subject in Cohort 1 will receive SYNT001 10 mg/kg weekly x 5 doses.

Subjects in Cohort 2 will receive SYNT001 10, 20 or 30 mg/kg weekly x 3 doses (Loading), followed by SYNT001 10, 20 or 30 mg/kg every other week x 5 doses (Maintenance). The Maintenance dose frequency may be increased to weekly (Cohort 2 alternative weekly maintenance schedule).

SYNT001 will be given as a 250-mL IV infusion over 1 hour ±15 minutes using a 0.2-micron, inline filter.

3.2.18 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.

3.2.19 Prior and Concomitant Medications

Prior to protocol amendment 5, all medications a subject received within 14 days prior to enrollment through the end of the study were documented. A history of treatments taken for primary disease, even if not taken within the 14 days prior to enrollment, were collected. After protocol amendment 5, all WAIHA treatments and all other treatments a subject receives within at least 3 months prior to screening through the end of study will be documented.

4. STATISTICAL METHODOLOGY

All descriptive and inferential statistical analyses will be performed using Statistical Analysis System (SAS®) software Version 9.3 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. 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 described using descriptive statistics: number of observations (n), mean, standard deviation (SD), median, Q1 (25^{th} percentile), Q3 (75^{th} percentile), minimum, and maximum. Geometric mean (GM) and GM CV will be provided for PK parameters.

Categorical data will be summarized using frequencies and percentages. 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.

4.2 Analysis Populations

Three sub-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 **PK population** will consist of all subjects who receive at least one dose of study drug and have post-dose PK data available. PK concentrations and parameters will be summarized based on the PK population.

- The **PD population** will consist of all subjects who receive at least one dose of study drug and have post-dose PD data available. PD data will be summarized based on the PD population.

Primary safety analyses will be performed on the Safety population. Demographics, subject disposition, and 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, and body mass index (BMI), age at diagnosis of WAIHA, WAIHA disease duration, and Karnofsky Performance Scale score (%).

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 subjects 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 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. Hematologic variables history will also be summarized. All medical/surgical history and hematologic variables history will also be listed.

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 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

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 visit 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, safety laboratory tests, vital sign measurements, PEs, 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
- TEAEs leading to discontinuation of study drug
- Drug-related TEAEs leading to discontinuation of study drug
- TEAEs leading to study drug interruption
- Drug-related TEAEs leading to study drug interruption
- TEAEs leading to study drug dose reduction
- Drug-related TEAEs leading to study drug reduction
- Death

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

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 drug) will be summarized separately.

TEAEs, SAEs, deaths and AEs leading to withdrawal, dose reduction, dose interruption, or treatment discontinuation 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 also 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 will be used.

Results, normal limits of the local laboratory, and abnormality flags will be listed.

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 will be used.

The arithmetic mean of parameters from triplicate ECGs will be calculated first for each participant at each planned time point. Then summary statistics for 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 changes (normal, abnormal not clinically significant, abnormal clinically significant) from pre-dose to each post-dose time point showing number and percentage of subjects with changes between categories will be presented by cohort.

The number and percentage of subjects experiencing potential QTcF prolongation (QTcF > 450, >480 and >500 msec, and change from baseline in QTcF >30 and >60 msec) will be summarized at each time point by cohort.

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

4.8 Analysis of Secondary Endpoints

4.8.1 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 serum concentration data will be used to calculate the following PK parameters, if feasible:

Parameters	**Description**
C_{max}	Maximum observed plasma concentration observed directly from data at Day 0 and Day 28
T_{max}	Time to reach maximum observed concentration directly from data at Day 0 and Day 28
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 at Day 0 and Day 28
$t_{½}$	Terminal elimination half-life, calculated as ln(2)/ λ_z at Day 0 and Day 28
AUC_{0-24}	AUC from time zero to 24 hours post-dose administration at Day 0 and Day 28
AUC_{∞}	AUC from time zero to infinity time (as $AUC_{0-t} + C_{last}/ \lambda_z$, where C_{last} is the last quantifiable concentration) at Day 0 and Day 28

Actual sampling time will be used for PK calculations. Actual sampling times that are outside the scheduled sampling times window described in Table 5 will be excluded from summary statistics of average PK SYNT001 serum concentrations but will still be used in the calculation of PK parameters.

PK parameters will be determined using non-compartmental method. 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_{∞} 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_{∞}) will not be calculated.

4.8.2 Pharmacodynamic / Disease Activity Analysis

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

Measurements for PD and disease activity biomarkers include:

- Total IgG assessments
- IgG subtypes (IgG1-4)
- Immunoglobulin A (IgA)
- Immunoglobulin M (IgM)
- Albumin levels
- CIC
- Hematocrit
- Hemoglobin
- Platelet count
- Reticulocyte count
- LDH
- Haptoglobin
- Direct Coombs tests
- Total and indirect bilirubin

PD/disease activity values, percentage change and absolute change from baseline will be summarized by cohort using descriptive statistics if result type is numerical. Mean (±SD) of values and percentage change and absolute change from baseline will be plotted by cohort. PD/disease activity result categories will be summarized if result type is categorical.

4.8.3 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 Analysis of Exploratory Endpoints

4.9.1 Exploratory Pharmacodynamic / Disease Activity Analysis

Exploratory PD and disease activity markers may include:

- D-dimer
- Antiphospholipid antibodies (lupus anticoagulant, anti-cardiolipin antibody, anti-beta-2-GP1 antibody)
- Antinuclear antibody titer
- Anti-dsDNA antibody titer
- Quantitative Coombs assay
- Cold agglutinins
- Fc gamma R2A receptor (FCGR2A)
- Complement component 3
- RNA sequencing
- Immunophenotyping including measurements of T cells, monocytes, natural killer (NK) cells, and B cells

All exploratory PD/disease activity data available at the time of the database lock 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.

4.9.2 Blood Transfusions

The number of units of packed red blood cells received by subjects will be summarized by cohort.

4.9.3 Corticosteroid Use

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

5. SAMPLE SIZE DETERMINATION

This study will be conducted in male and female subjects with a confirmed diagnosis of WAIHA. 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.

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 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. Footnotes in listings will reference datasets used in the listing. Footnotes in tables and figures will reference the appurtenant listings.

7. 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.

8. APPENDICES

Appendix A: Study Assessment

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 (or ET)**
Time Point (Study Day)	**−14 to −1**	**0**	**1 (±1 h)**	**2 (±2 h)**	**5[a] (±4 h)**	**7 (±6 h)**	**12[a] (±6 h)**	**14 (±6 h)**	**19[a] (±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 (±5 d)**
Informed consent	X																	
Demographics/medical history	X																	
Inclusion/exclusion	X																	
Physical examination[b]	X	X				X		X		X	X				X	X	X	X
Vital signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Karnofsky Performance Scale	X																	
Pulse oximetry[d]		X				X		X		X	X							
Clinical safety labs[e]	X	X				X		X		X	X			X	X	X	X	X
Pregnancy test[f]	X	X														X		X
Hepatitis and HIV antibody screen	X																	
12-lead ECG[g]	X	X					X				X					X		
Tetanus and VZV antibodies[h]		X														X	X	X
Cold agglutinins (titer and thermal amplitude)		X												X		X	X	X
PK sampling[i]		X	X	X	X						X	X	X	X				
Immunogenicity[j]		X						X			X					X	X	X
Study drug administration[k]		X				X		X		X	X							
Immunoglobulins[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[m]	X[m]
CIC		X			X	X	X	X	X	X	X			X	X	X	X	X
Haptoglobin	X	X				X		X		X	X			X	X	X	X	X
Direct Coombs test	X	X						X						X		X	X	X
Additional PD sample collection[n]		X						X						X		X	X	X
FCGR2A by buccal swab[o]		X																
RNA sequencing		X						X						X		X	X	X
Urine IgG		X						X						X		X	X	X

Immunophenotyping[p]		X									X					X		
Quantitative Coombs assay		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 at least 3 months prior to screening through the last study visit*																

CIC = circulating immune complexes; d = day(s); ECG = electrocardiogram; ET = early termination; h = hour(s); *FCGR2A* = Fc gamma R2a receptor; HIV = human immunodeficiency virus; ICF = informed consent form; Ig = immunoglobulin; PD = pharmacodynamic; PK = pharmacokinetic; VZV = varicella-zoster virus.

a. Visit Days 5, 12, and 19 may be conducted via at-home nurse in lieu of a subject visit to the study site.
b. Complete physical examination, including weight, to be performed. Height and body mass index will be additional assessments conducted at screening.
c. 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.
d. 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.
e. Clinical safety labs: hematology, clinical chemistry, and urinalysis. See Protocol Section 6.7 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. PD markers (albumin levels, hematocrit, hemoglobin, platelet count, reticulocyte count, lactate dehydrogenase, and total and indirect bilirubin) will be derived from the clinical safety laboratory results.
f. 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.
g. 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 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.
h. 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 6.7.3 for additional information.
i. 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 6.7.4 for additional information.
j. 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 Protocol Section 6.7.6 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 9 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.
m. 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.
n. Additional PD samples to be collected for measurements of biomarkers, including D-dimer; antiphospholipid antibodies (lupus anticoagulant, anti-cardiolipin, and anti-beta-2-GP1 antibodies); antinuclear antibody titer; anti-double-stranded DNA antibody titer; complement component 3. See Protocol Section 6.7.5 for complete information.
o. Buccal samples to be collected and stored.
p. Immunophenotyping by flow cytometry for measurement of $CD3^+CD4^+$ T, $CD3^+CD8^+$ T, monocytes, natural killer (NK) cells, and B cells.

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)	**−28 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
Karnofsky Performance Scale	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
Pregnancy test[e]	X	X			X					X		X
Hepatitis and HIV antibody screen	X											
12-lead ECG[f]	X	X		X	X					X		X
Tetanus and VZV antibodies[g]		X			X					X		X
Cold agglutinins (titer and thermal amplitude)		X			X					X		X
PK sampling[h]		X	X	X	X				X			
Immunogenicity[i]	X	X	X	X	X	X	X	X	X	X	X	X
Study drug administration[j]		X	X	X	X	X	X	X	X			
Immunoglobulins[k]	X	X	X	X	X	X	X	X	X	X[l]	X[l]	X[l]
CIC		X	X	X	X	X	X	X	X	X	X	X
Haptoglobin	X	X	X	X	X	X	X	X	X	X	X	X
Direct Coombs test	X	X		X	X					X		X
Additional PD sample collection[m]		X			X					X		
FCGR2A by buccal swab[n]		X										
RNA sequencing		X			X					X		

Immunophenotyping[o]		X			X					X		
Quantitative Coombs assay		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 at least 3 months prior to screening 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; ICF = informed consent form; Ig = immunoglobulin; PD = pharmacodynamic; 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 day, 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 6.7 for a complete list. Full clinical safety lab draws will be collected at screening and at all study visits prior to infusion if applicable. PD markers (albumin levels, hematocrit, hemoglobin, platelet count, reticulocyte count, lactate dehydrogenase, and total and indirect bilirubin) will be derived from the clinical safety laboratory results.
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 6.6 for additional information. On days of treatment, to be obtained 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 6.7.3 for additional information.
h. 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 6.7.4 for additional information.
i. Immunogenicity: Samples will be collected pre-dose when collected on dosing days. See Protocol 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 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 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 dosing days, samples are collected prior to infusion of study drug. See Protocol Section 6.7.5 for additional information.
l. Subjects will return to the clinic on Days 91, 112, and 140 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 Day 140 will be referred for further management.
m. Additional PD samples to be collected for measurements of biomarkers, including D-dimer; antiphospholipid antibodies (lupus anticoagulant, anti-cardiolipin, and anti-beta- 2-GP1 antibodies); antinuclear antibody titer; anti-double-stranded DNA antibody titer; complement component 3. Collect samples pre-dose on dosing days. See Protocol Section 6.7.5 for additional information.
n. Buccal samples to be collected and stored.
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.

Table 4. Study Assessments for Cohort 2; Alternative Weekly Maintenance Schedule

	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)	**−28 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[q]**
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
Karnofsky Performance Scale	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
Pregnancy test[e]	X	X			X										X		X
Hepatitis and HIV antibody screen	X																
12-lead ECG[f]	X	X		X	X										X		X
Tetanus and VZV antibodies[g]		X			X										X		X
Cold agglutinins (titer and thermal amplitude)		X			X										X		X
PK sampling[h]		X	X	X	X									X			
Immunogenicity[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug administration[j]		X	X	X	X	X	X	X	X	X	X	X	X	X			
Immunoglobulins[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[l]	X[l]	X[l]
CIC		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Haptoglobin	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Direct Coombs test	X	X		X	X										X		X
Additional PD sample collections[m]		X			X										X		

FCGR2A by buccal swab[n]		X															
RNA sequencing		X			X										X		
Immunophenotyping[o]		X			X										X		
Quantitative Coombs assay		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 at least 3 months prior to screening 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; ICF = informed consent form; Ig = immunoglobulin; PD = pharmacodynamic; 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 6.7 for a complete list. Full clinical safety lab draws will be collected at screening and at all study visits prior to infusion. PD markers (albumin levels, hematocrit, hemoglobin, platelet count, reticulocyte count, lactate dehydrogenase, and total and indirect bilirubin) will be derived from the clinical safety laboratory results.
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 6.6 for additional information. On dosing 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 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 6.7.3 for additional information.
h. 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 Protocol Section 6.7.4 for additional information.
i. Immunogenicity: Samples will be collected pre-dose when collected on dosing days. See Protocol 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 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 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 dosing days, samples are collected prior to infusion of study drug. See Protocol Section 6.7.5 for additional information.
l. Subjects will return to the clinic on Days 91, 112, and 140 or ET 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 Day 140 will be referred for further management.
m. Additional PD samples to be collected for measurements of biomarkers, including D-dimer; antiphospholipid antibodies (lupus anticoagulant, anti-cardiolipin, and anti-beta- 2-GP1 antibodies); antinuclear antibody titer; anti-double-stranded DNA antibody titer; complement component 3. Collect samples pre-dose on dosing days. See Protocol Section 6.7.5 for additional information.
n. Buccal samples to be collected and stored.
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

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 post end-of-infusion	±60 minutes	N/A
48 hours post end-of-infusion	±120 minutes	N/A
Pharmacodynamic (Immunoglobulins) Sampling		
0 hour	−240 minutes to 0 hour	−240 minutes to 0 hour
24 hours post end-of-infusion	±60 minutes	N/A
48 hours 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, 60, and 120 minutes post end-of-infusion	±10 minutes	±10 minutes

Abbreviations: ECG = electrocardiogram; PD = pharmacodynamic; PK = pharmacokinetic.

[a]Vital signs to include blood pressure, pulse rate, respiratory rate, oral temperature, and pulse oximetry (Cohort 1 only).

Table 6. 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, 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, 140
Albumin Hematocrit Hemoglobin Haptoglobin Platelet count Reticulocyte count Lactate dehydrogenase (LDH) Total and indirect bilirubin	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, 140
Direct Coombs test (also known as direct antiglobulin test [DAT])	Screening and Days 0, 14, 33, 56, 84, and 112	Screening and Days 0, 14, 28, 91, 140
D-dimer Antiphospholipid antibodies Lupus anticoagulant Anti-cardiolipin antibody Anti-beta-2-GP1 antibody Antinuclear antibody (ANA) titer Anti-dsDNA antibody titer Complement component 3 (C3)	Days 0, 14, 33, 56, 84, and 112	Days 0, 28, 91
RNA sequencing	Days 0, 14, 33, 56, 84, and 112	Days 0, 28, 91
Urine IgG	Days 0, 14, 33, 56, 84, and 112	NA
Quantitative Coombs assay	Days 0, 14, 33, and 56	Days 0, 14, 28, 91
Immunophenotyping by flow cytometry for measurement of; • $CD3^+CD4^+$ T • $CD3^+CD8^+$ T • monocytes • NK cells • B cells	Days 0, 28, and 56	Days 0, 28, 91
Cold agglutinins (titer and thermal amplitude)	Days 0, 33, 56, 84, and 112	Days 0, 28, 91, 140
FCGR2A SNP by buccal swab	Day 0	Day 0

a Ongoing safety and PD evaluations may result in modification of the dosing regimen from every other week to weekly.

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.