# 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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| **Unique Protocol ID:** | **SYNT001-102** |
| **NCT Number:** | **NCT03075878** |
| **Date of Protocol:** | **23 October 2018** |

# SYNTIMMUNE, INC.

# CLINICAL STUDY PROTOCOL

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

**Protocol Number:** SYNT001-102
**IND Number:** 128152
**Study Drug:** SYNT001
**Sponsor:** Syntimmune, Inc.
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**Original Protocol:** 19 December 2016
**Amendment 1.1:** 18 January 2017
**Amendment 2.0** 12 April 2017
**Amendment 3.0** 10 October 2017
**Amendment 4.0** 21 December 2017
**Amendment 5.0** 23 October 2018

# SPONSOR SIGNATURE

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

PPD

PPD
Syntimmune, Inc.

Date of Signature

# INVESTIGATOR SIGNATURE

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

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care under applicable regulations.

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|---|---|
| Investigator Signature | Date of Signature |

Name of Investigator (please print)

# 1. SYNOPSIS

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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) |
| **Protocol number** | SYNT001-102 |
| **Number of study centers** | Approximately 15 global study sites |
| **Clinical phase** | Phase 1b/2 |
| **Study background** | SYNT001, a humanized, affinity-matured IgG4-kappa monoclonal antibody (mAb), blocks immunoglobulin G (IgG) and IgG immune complex (IC) interactions with the neonatal crystallizable fragment receptor (FcRn) and thereby inhibits the varied roles of FcRn in immune response.<br><br>Through specific and high affinity blockade of FcRn, SYNT001 has been shown to increase the catabolism of IgG and IgG IC in healthy volunteers and is predicted to block the ability of IgG IC to activate intracellular signaling events associated with binding to FcRn. This predicts that SYNT001 will also accelerate degradation of endogenous circulating IgG autoantibodies and IgG IC specifically involved in the pathogenesis of autoimmunity. Blocking FcRn interactions with IgG ICs further predicts that SYNT001 will have consequences for innate and adaptive cellular immunity. In the first instance, blocking multimeric IgG IC's interactions with FcRn within antigen-presenting cells should result in inhibition of IC-mediated inflammatory cytokine production and release by these cells. In addition, as FcRn determines the intracellular itinerary of IgG ICs within and among compartments important in cellular immunity, it is further anticipated that SYNT001 will block antigen processing and presentation of antigens contained within ICs that would otherwise lead to $CD8^+$ and $CD4^+$ T cell activation. Thus, SYNT001 is expected to specifically target immune functions associated with IgG and IC that are involved in certain IgG-mediated autoimmune conditions.<br><br>SYNT001 targets key mechanisms contributing to pathology in a variety of IgG-mediated autoimmune disorders. While current treatments for certain autoimmune disorders, including chronic steroids, immunosuppressants, intravenous (IV) immunoglobulin (IVIG), plasmapheresis, and anti-CD20 mAbs, such as rituximab, can be effective, they are associated with significant adverse effects, and delayed or non-durable responses.<br><br>IgG autoantibodies directed against red blood cells (RBCs) are considered to play a central role in the hemolysis and anemia observed in patients with warm autoimmune hemolytic anemia (WAIHA). SYNT001 is a humanized IgG4 mAb that blocks IgG interactions with FcRn that would be anticipated to affect pathogenic behavior of IgG autoantibodies. Administration of SYNT001 significantly decreases total IgG levels, including a corresponding decrease in the levels of the pathogenic autoantibodies. This may lead to a decrease in the IgG coating of RBCs and the interaction of IgG-coated RBCs with FcRn in phagocytic cells, leading to decreased hemolysis in WAIHA patients with active hemolysis. Moreover, the ability of SYNT001 to reduce circulating immune complexes (CICs) and the associated innate and adaptive immune responses may allow for sustained |

<table>
<tr><td></td><td colspan="2">disease modification.</td></tr>
<tr><td>Study rationale</td><td colspan="2">This study is being conducted to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity, and effects of IV SYNT001 in subjects with WAIHA.</td></tr>
<tr><td>Study objectives and endpoints</td><td colspan="2">The study objectives and their corresponding endpoints (primary, secondary, and exploratory) are detailed below.
<table>
<tr><th>Primary Objective</th><th>Primary Endpoint</th></tr>
<tr><td>Safety: To evaluate the safety and tolerability of IV infusions of SYNT001 at different dose levels and dosing regimens in subjects with WAIHA</td><td>Safety: The evaluation of SYNT001 safety based on vital signs, physical examinations, electrocardiograms (ECGs), clinical safety laboratory tests, the incidence of adverse events (AEs), treatment-emergent adverse events (TEAEs), and serious adverse events (SAEs) summarized by dose and dosing regimen, severity, and relationship to study drug</td></tr>
<tr><th>Secondary Objective</th><th>Secondary Endpoint</th></tr>
<tr><td>To evaluate the efficacy of doses of SYNT001 at different dose levels and dosing regimens on PD biomarkers</td><td>The evaluation of PD biomarkers based on absolute serum levels and percent change from baseline of total IgG, IgG subtypes (IgG1-4), immunoglobulin A (IgA), immunoglobulin M (IgM), albumin, and CIC summarized by dose, dosing regimen and time point</td></tr>
<tr><td>To determine the PK of SYNT001 following IV infusions at different dose levels and dosing regimens</td><td>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 and time point</td></tr>
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| 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<br>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 |
| **Exploratory Objectives** | **Exploratory Endpoint** |
| 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:<br>• D-dimer<br>• Antiphospholipid antibodies (lupus anticoagulant, anti-cardiolipin antibody, anti-beta-2-GP1 antibody)<br>• Antinuclear antibody titer<br>• Anti-dsDNA antibody titer<br>• Quantitative Coombs assay<br>• Cold agglutinins (titer and thermal amplitude)<br>• Fc gamma R2A receptor (FCGR2A) single nucleotide polymorphisms (SNP) by genotyping<br>• Complement component 3 levels by nephelometry<br>• Presence of disease and inflammatory markers by total RNA sequencing<br>• Immunophenotyping including measurements of T cells, monocytes, natural killer (NK) cells, and B cells by flow |

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| | 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 |
| **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.<br>Up to 8 subjects with a diagnosis of WAIHA will receive SYNT001 10 mg/kg weekly x 5 doses (Cohort 1).<br>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) (Cohort 2). For Cohort 1 details of the dosing schedule and assessments, see Table 2. For Cohort 2 details, see Table 3. An alternative weekly maintenance schedule of assessment for Cohort 2 is presented in APPENDIX 3, Table 10.<br>Subjects in both cohorts will complete the following periods of assessment: Screening, Treatment, and Follow-Up.<br>Up to 8 subjects may be enrolled in Cohort 1. After 4 subjects reach Day 42, the Sponsor Medical Team will review available safety and PD data and will decide the dosing regimen for Cohort 2. The maintenance dose frequency may be increased to weekly (Cohort 2 alternative weekly maintenance schedule). Dosing regimen decisions for Cohort 2 will be communicated to the sites prior to Day 0 dosing.<br>The Sponsor Medical Team will consist of at least the Medical Monitor and the Sponsor Medical Lead. The Sponsor Medical Team may request that Investigators, other experts, or members within their organization participate in the review.<br>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:<br>10, 20 or 30 mg/kg<br>Maintenance:<br>10, 20 or 30 mg/kg | 3<br><br>5 | Weekly<br><br>Every other week |

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| 2<br>Alternative weekly schedule | Up to 12 | Loading:<br>10, 20 or 30 mg/kg<br>Maintenance:<br>10, 20 or 30 mg/kg | 3<br><br>10 | Weekly<br><br>Weekly |

Subjects in Cohorts 1 and 2 will be enrolled at staggered intervals to facilitate adequate safety evaluation before dosing of subsequent subjects may proceed.

At 24-hour and 7-day intervals described below, available safety data (including, but not limited to, dose-limiting toxicities [DLTs], AEs, TEAEs, SAEs), and PD (including, but not limited to, total IgG levels) will be reviewed.

**Safety Review of 24-hour Data for Cohorts 1 and 2, Subject 1**

- The first 2 subjects will be dosed at least 24 hours apart. A Dose Escalation Committee (DEC) 24-hour safety data review for the first subject in Cohort 1 will be performed to ensure that there are no overt safety concerns before dosing the second subject. The Sponsor Medical Team will conduct the 24-hour safety data review for the first subject in Cohort 2.

**Safety Review of 7-day Data for Cohorts 1 and 2, Subjects 1 and 2**

- The 7-day safety data for the first 2 subjects in Cohort 1 will be performed by the DEC prior to dosing the remaining subjects in the cohort.
- The 7-day safety data for the first 2 subjects in Cohort 2 will be performed by the Sponsor Medical Team prior to dosing the remaining subjects in the cohort.

The 24-hour and 7-day reviews will consider seriousness and severity of AEs/TEAEs/SAEs and relatedness to study drug, vital sign assessments, physical examinations, and clinical laboratory testing.

Safety (including but not limited to DLTs, AEs, TEAEs, and SAEs), and PD (including but not limited to IgG levels) data will be reviewed on an ongoing basis by the Sponsor Medical Team. In addition, at any point a review of all cumulative data may be performed.

- If a DLT occurs, dosing will be halted within that cohort and dose escalation will not occur. NOTE: DLTs will be defined generally as severe (Grade 3) AEs occurring in ≥2 subjects that are determined to be clinically significant and considered related to study drug.
- If any subject at any time during the study experiences a life-threatening AE (Grade 4) that is considered related to study drug, further dosing in all enrolled subjects will be suspended.
- At any time during the study, the study or any ongoing study cohort may be discontinued if the Sponsor Medical Team determines that further drug exposure would pose an undue risk to subjects.

Dosing for any individual subject will be discontinued (ie, no further

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| | administration of SYNT001) if the subject experiences any study drug-related SAE or any study drug-related non-serious AE that, in the judgement of the Investigator (following consultation with the Medical Monitor, if desired), or in the judgement of the Sponsor Medical Team, suggests that it could be unsafe to administer further study drug to that subject. |
| **Number of subjects** | Up to 20 subjects are planned; up to 8 subjects in Cohort 1 and up to 12 subjects in Cohort 2. Subjects who withdraw for any reason other than an AE may be replaced. |
| **Study population** | Male or female subjects 18 years of age or older with a confirmed diagnosis of WAIHA |
| **Diagnosis and main entry criteria** | **Inclusion criteria:**<br>Subjects must meet the following criteria to be eligible for the study:<br>1. Willing and able to read, understand and sign an informed consent form.<br>2. Male or female ≥18 years of age at the time of screening.<br>3. Confirmed diagnosis by enrolling physician of WAIHA, including positive direct Coombs test.<br>4. Hemoglobin <11 g/dL<br>5. Evidence of active hemolysis, including any one of the below:<br>a. LDH >upper limit of normal (ULN) or<br>b. Haptoglobin <lower limit of normal (LLN) or<br>c. Indirect bilirubin >ULN.<br>6. Other treatments for WAIHA:<br>a. If treated with rituximab or other anti-CD20 mAb, last dose >3 months prior to screening (a dose is defined as ≥10% of the intended dose).<br>b. If being treated with other immunosuppressants (ie, azathioprine, mycophenolate mofetil, methotrexate, cyclosporine, tacrolimus, sirolimus, or low-dose oral cyclophosphamide [≤100 mg/day]), dose must be stable (<25% change in dose) for 4 weeks prior to screening.<br>c. If being treated with corticosteroids, dose must be ≤1 mg/kg/day of prednisone or equivalent, and the dose may not be increased by more than 50% in the 2 weeks prior to screening.<br>d. No pulse corticosteroids are allowed in the 2 weeks prior to screening.<br>7. Treatment of chronic lymphocytic leukemia (CLL) or non-Hodgkin lymphoma (NHL) must be:<br>a. Food and Drug Administration (FDA)-approved for oral treatment, and<br>b. Stable (<10% change in dose) for 6 weeks prior to screening; Bruton's tyrosine kinase inhibitor dose must be stable (<10% change in dose) for 8 weeks prior to screening.<br>8. Body mass index (BMI) >18.5 kg/$m^2$.<br>9. Has a negative pregnancy test (for women of childbearing potential) documented prior to the first dose of study drug.<br>10. Females of childbearing potential must agree to be abstinent or else use any two of the following medically acceptable forms of contraception |

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| | (<1% per year failure rate) from the screening period through the final study visit: oral contraceptive, condom with or without spermicidal jelly, diaphragm or cervical cap with spermicidal jelly, or intra-uterine device (IUD). A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception.<br>11. Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months do not require contraception during the study.<br>12. Males with female partners of childbearing potential, including males who are surgically sterile (post vasectomy), must agree to be abstinent or else use a medically acceptable form of contraception from the screening period through the final study visit. |
| | **Exclusion criteria:**<br>Subjects meeting any of the following criteria are ineligible for the study:<br>1. Subject unable or unwilling to comply with the protocol.<br>2. Active non-hematologic malignancy or history of non-hematologic malignancy in the 3 years prior to screening (exclusive of non-melanoma skin cancer and cervical cancer in situ).<br>3. Karnofsky Performance Scale ≤50.<br>4. Estimated glomerular filtration rate (eGFR) <45 mL/minute/1.73 $m^2$.<br>5. Platelet count <30 $\times 10^9$/L.<br>6. Corrected reticulocyte count <2% (using the following calculation; (% reticulocyte x % hematocrit) / normal hematocrit [45%]).<br>7. Positive for human immunodeficiency virus (HIV) or hepatitis C antibody.<br>8. Positive for hepatitis B surface antigen.<br>9. Splenectomy within 3 months of screening.<br>10. Any T-cell or NK-cell NHL, and any moderate- or high-grade B-cell lymphoma, including Burkitt lymphoma, lymphoblastic B-cell lymphoma, diffuse large B-cell lymphoma, mantle cell lymphoma, or small non-cleaved cell non-Burkitt lymphoma.<br>11. Received any cytotoxic (other than azathioprine, chlorambucil, low-dose methotrexate, or low-dose oral cyclophosphamide [≤100 mg/day]) or any non-anti-CD20 mAb therapy in the 3 months prior to screening.<br>12. Any exposure to an investigational drug or device within the 30 days prior to screening.<br>13. IVIG treatment within 30 days of screening.<br>14. Plasmapheresis or immunoadsorption within 30 days of screening.<br>15. Cellular therapy, including chimeric antigen receptor T-cell (CAR-T), at any time prior to screening.<br>16. Use of any immunosuppressive drugs within 3 months of screening, not including those allowed by the inclusion criteria.<br>17. Active infection or history of recurrent infections.<br>18. Serum total IgG <600 mg/dL.<br>19. Subject has any current medical condition that, in the opinion of the Investigator, may compromise their safety or compliance, preclude successful conduct of the study, or interfere with interpretation of the results (eg, a significant pre-existing illness or other major comorbidity that the Investigator considers may confound the interpretation of the |

<table>
<tr><td></td><td>study results).<br>20. Any vaccination within 2 weeks of screening.</td></tr>
<tr><td>Study drug, dosage, and administration</td><td>Study drug: SYNT001<br>Dosage:<br>Cohort 1: 10 mg/kg weekly x 5 doses<br>Cohort 2: 10, 20 or 30 mg/kg weekly x 3 doses (Loading) followed by 10, 20 or 30 mg/kg every other week x 5 doses (Maintenance).<br>Up to 8 subjects may be enrolled in Cohort 1. After 4 subjects reach Day 42, the Sponsor Medical Team will review available safety and PD data and will decide the dosing regimen for Cohort 2. The Maintenance dose frequency may be increased to weekly (Cohort 2 alternative weekly maintenance schedule).<br>Product presentation and preparation: SYNT001 is provided as a liquid at a nominal concentration of 50 mg/mL. SYNT001 is diluted in dextrose 5% in water (D5W) to prepare the solution for infusion.<br>Route of administration: IV in 250 mL over 1 hour ±15 minutes. Investigators may adjust the duration of the infusion if needed to increase tolerability.</td></tr>
<tr><td>Control, dose, and route of administration</td><td>Not applicable</td></tr>
<tr><td>Duration of subject participation</td><td>The duration of subject participation for each cohort is as follows:
<table>
<tr><th rowspan="2">Cohort</th><th rowspan="2">Screening</th><th rowspan="2">Treatment</th><th rowspan="2">Follow-up</th><th colspan="2">Maximum Total</th></tr>
<tr><th>Days</th><th>Weeks</th></tr>
<tr><td>1</td><td>≤14 days</td><td>28 days</td><td>84 days</td><td>126 days</td><td>18 weeks</td></tr>
<tr><td>2</td><td>≤28 days</td><td>84 days</td><td>56 days</td><td>154 days</td><td>22 weeks</td></tr>
</table></td></tr>
<tr><td>Permitted and prohibited concomitant treatments</td><td>All WAIHA treatments and all other treatments a subject receives within at least 3 months prior to screening through the end of the study will be documented.<br>Permitted medications:<br>Concomitant medication and treatment for co-existing conditions, including those for WAIHA, are permitted if not listed as prohibited.<br>1. Concomitant treatment that is medically indicated for any AEs the subject experiences during the study.<br>2. Medication for potential infusion-related reactions (IRRs), including post-infusion headache: the Investigator may recommend prophylactic use of acetaminophen, IV hydration, diphenhydramine, or histamine$_2$ blockers (eg, ranitidine, famotidine).<br>3. Stable regimen of the following systemic immunosuppressants: azathioprine, mycophenolate mofetil, low-dose methotrexate, cyclosporine, tacrolimus, sirolimus, corticosteroids, or low-dose oral cyclophosphamide (≤100 mg/day).<br>Prohibited medications:<br>Use of the following medications will not be permitted during the study unless specified above as permitted:<br>1. Rituximab or other anti-CD20 antibody<br>2. Monoclonal antibodies other than study drug</td></tr>
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| | 3. Any immunosuppressive drugs apart from those that are listed as permitted<br>4. Any cytotoxic agent other than azathioprine, chlorambucil, low-dose methotrexate, or low-dose oral cyclophosphamide (≤100 mg/day)<br>5. IV corticosteroids prior to infusion of study drug (except in subjects who received corticosteroids for treatment of a prior infusion reaction to SYNT001).<br>6. Any investigational drug or device<br>7. Vaccinations within 2 weeks of screening through 28 days following the final dose of study drug.<br><br>**WAIHA Co-medication:**<br>Subjects receiving WAIHA treatment at enrollment, should remain on a stable treatment regimen throughout dosing and for the 14 days after the last dose of SYNT001.<br><br>**Corticosteroids**<br><u>Before enrollment</u><br>The dose of corticosteroids taken for WAIHA or any other condition prior to screening must be at a dose <u>≤</u>1 mg/kg and the dose level must have not increased in dose level by more than 50% in the 2 weeks prior to screening. No pulse dosing of steroids is permitted in the 2 weeks prior to screening.<br><u>From screening until 2 weeks after the last dose of SYNT001</u><br>The dose of corticosteroids taken for WAIHA or any other condition should remain stable (<10% change in dose level) from screening until 2 weeks after the last dose of SYNT001. Corticosteroids should neither be started nor discontinued during this period with the exception of subjects who experience an IRR that requires corticosteroids as part of the management of the IRR. Such subjects may receive corticosteroids prophylactically prior to subsequent SYNT001 infusions at the discretion of the Investigator.<br><br><u>From 2 weeks after the last dose of SYNT001 until end of study participation</u><br>At the discretion of the Investigator, but only after at least 2 weeks beyond the last dose of SYNT001, a slow corticosteroid taper may be started as per the following suggested schedule:<br>• If on >30 mg of prednisone per day, decrease by no more than 10 mg every two weeks until a final dose.<br>If per the Investigator's judgement, the subject would benefit from a change to the WAIHA treatment beyond the allowed steroid taper, this will be considered on a case-by-case basis in consultation with the Sponsor. |
| **Statistical considerations** | Three populations will be employed in the analysis of study data:<br>• The Safety population will consist of all subjects who have received at least one dose of study drug.<br>• The PK population will consist of all subjects who receive at least one dose of study drug and have post-dose PK data available.<br>• The PD population will consist of all subjects who receive at least |

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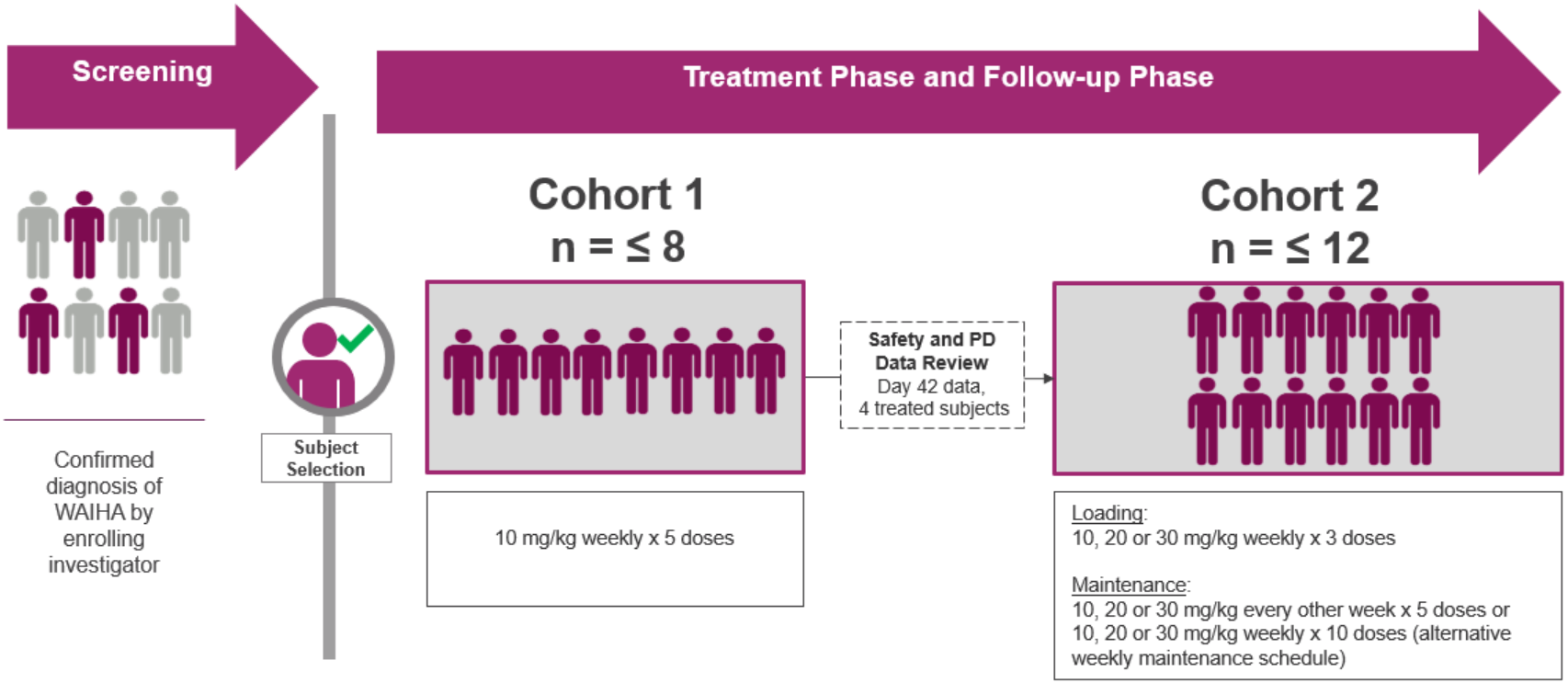
| | one dose of study drug and have post-dose PD data available.<br><br>Primary safety analyses will be performed on the Safety population. Demographics, subject disposition, and screening and baseline characteristics will be summarized for the Safety, PK and PD populations, where appropriate.<br>**Sample size**<br>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.<br>**Statistical methodology**<br>Treatment-emergent AEs (TEAEs) will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA®; Version 19 or higher) System Organ Class (SOC) and preferred term, classified from verbatim terms. The incidence and percentage of subjects with at least one occurrence of a preferred term will be included, using the most severe grade. The number of events per preferred term will also be summarized. Causality (relationship to study drug [related/not related]) will be summarized separately.<br>TEAEs, SAEs, and AEs leading to withdrawal, dose modification, or treatment discontinuation will be listed by subject using SOC and preferred terms. Duration of AEs will be determined and included in listings, along with action taken and outcome.<br>Laboratory results will be summarized by time point, dose, and dose regimen. The incidence of laboratory abnormalities will be summarized. The worst on-study grade after the first dose of study drug will be summarized. Results for variables that are not coded will be presented in the listings as below, within, or above the normal limits of the central laboratory. Vital sign measurements and change from baseline will be summarized at each scheduled time point by using descriptive statistics. PD/PK results will be summarized by dose and dose regimen. Descriptive statistics of PD/PK parameters for SYNT001 will include mean, standard deviation (SD), coefficient of variation (CV), median, minimum, and maximum.<br>Immunogenicity results will be summarized by cohort and time point. Descriptive statistics will include mean, SD, CV, median, minimum, and maximum.<br>Disease activity marker results (hematocrit, hemoglobin, platelet count, reticulocyte count, LDH, haptoglobin, total and indirect bilirubin, and direct Coombs test) will be summarized by dose and dose regimen. Descriptive statistics will include mean, SD, median, minimum, and maximum.<br><br>Final statistical analyses details will be documented in the statistical analysis plan. |

**Figure 1. Cohort Enrollment**




WAIHA = warm autoimmune hemolytic anemia

## 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 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 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 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 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 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 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 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 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 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 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 Section 6.7.4 for additional information.

i. **Immunogenicity:** Samples will be collected pre-dose when collected on dosing days. See Section 6.7.6 for additional information.

j. Prior to **study drug infusion**, SYNT001 drug product is to be diluted in dextrose 5% in water to a total volume of 250 mL and administered intravenously over 1 hour ±15 minutes using a 0.2-micron, inline filter. See Section 9 for additional information.

k. **Immunoglobulins (IgG, IgA, IgM) and IgG subtypes (IgG 1-4):** Collected for measurements of IgG, IgG subtypes (IgG1-4), IgA, and IgM at every visit. On dosing days, samples are collected prior to infusion of study drug. See 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 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.

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| | |
|---|---|
| ADA | anti-drug antibodies |
| AE | adverse event |
| ALT | alanine aminotransferase |
| ANA | antinuclear antibody |
| AST | aspartate aminotransferase |
| ATC | Anatomical Therapeutic Chemical |
| $AUC_{0-24}$ | area under the serum concentration-time curve from pre-dose (time 0) to 24 hours post-dose |
| $AUC_{0-\infty}$ | area under the serum concentration-time curve from pre-dose (time 0) to infinity |
| BLQ | below the limit of quantification |
| BMI | body mass index |
| BUN | blood urea nitrogen |
| CAR-T | chimeric antigen receptor and T-cell |
| CFR | Code of Federal Regulations |
| C3 | complement component 3 |
| CBC | complete blood count |
| CIC | circulating immune complexes |
| CLL | chronic lymphocytic leukemia |
| $C_{max}$ | maximum serum concentration determined directly from the concentration-time profile |
| CRO | contract research organization |
| CV | coefficient of variation |
| D5W | dextrose 5% in water |
| DAT | direct antiglobulin test |
| DEC | Dose Escalation Committee |
| DLT | dose-limiting toxicity |
| DNA | deoxyribonucleic acid |
| dsDNA | double-stranded deoxyribonucleic acid |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| eGFR | estimated glomerular filtration rate |
| ET | early termination |
| *FCGR2A* | Fc gamma R2a receptor |
| FcRn | neonatal Fc receptor |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GI | gastrointestinal |
| GLP | Good Laboratory Practice |

| | |
|---|---|
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | human immunodeficiency virus |
| IB | Investigator's Brochure |
| IC | immune complex |
| ICF | informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IgA | immunoglobulin A |
| IgG | immunoglobulin G |
| IgM | immunoglobulin M |
| IND | investigational new drug |
| IRB | institutional review board |
| IRR | infusion-related reaction |
| IUD | intrauterine device |
| IV | intravenous |
| IVIG | intravenous immunoglobulin |
| LDH | lactate dehydrogenase |
| LLN | lower limit of normal |
| mAb | monoclonal antibody |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NCI CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NHL | non-Hodgkin lymphoma |
| NHP | non-human primate |
| NK | natural killer |
| NOAEL | no-observed-adverse-effect level |
| NSAID | non-steroidal anti-inflammatory drug |
| PD | pharmacodynamics |
| PK | pharmacokinetic |
| RBC | red blood cells |
| RNA | ribonucleic acid |
| RNAseq | RNA sequencing |
| QTcF | corrected QT interval using Fridericia's formula |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SAS | Statistical Analysis System |
| SD | standard deviation |
| SNP | single nucleotide polymorphism |
| SOC | system organ class |
| SOP | standard operating procedures |

| | |
|---|---|
| SYNT001 | a humanized, affinity matured IgG4-kappa monoclonal antibody |
| $t_{1/2}$ | Half-life |
| TEAE | treatment-emergent adverse event |
| $T_{max}$ | observed time to reach peak serum concentration |
| ULN | upper limit of normal |
| UNS | unscheduled |
| US | United States |
| VZV | Varicella-Zoster virus |
| WAIHA | warm autoimmune hemolytic anemia |
| WHO | World Health Organization |
| WHO-DD | World Health Organization Drug Dictionary |

# 2. BACKGROUND AND RATIONALE

SYNT001, a humanized, affinity-matured IgG4-kappa monoclonal antibody (mAb), blocks immunoglobulin G (IgG) and IgG immune complex (IC) interactions with the neonatal crystallizable fragment receptor (FcRn) and thereby inhibits the varied roles of FcRn in immune response.

Through specific and high affinity blockade of FcRn, SYNT001 has been shown to increase the catabolism of IgG and IgG IC in healthy volunteers and is predicted to block the ability of IgG IC to activate intracellular signaling events associated with binding to FcRn. This predicts that SYNT001 will also accelerate degradation of endogenous circulating IgG autoantibodies and IgG IC specifically involved in the pathogenesis of autoimmunity. Blocking FcRn interactions with IgG ICs further predicts that SYNT001 will have consequences for innate and adaptive cellular immunity. In the first instance, blocking multimeric IgG IC's interactions with FcRn within antigen-presenting cells should result in inhibition of IC-mediated inflammatory cytokine production and release by these cells. In addition, as FcRn determines the intracellular itinerary of IgG ICs within and among compartments important in cellular immunity, it is further anticipated that SYNT001 will block antigen processing and presentation of antigens contained within ICs that would otherwise lead to $CD8^+$ and $CD4^+$ T cell activation. Thus, SYNT001 is expected to specifically target immune functions associated with IgG and IC that are involved in certain IgG-mediated autoimmune conditions.

SYNT001 targets key mechanisms contributing to pathology in a variety of IgG-mediated autoimmune disorders. While current treatments for certain autoimmune disorders, including chronic steroids, immunosuppressants, intravenous (IV) immunoglobulin (IVIG), plasmapheresis, and anti-CD20 mAbs, such as rituximab, can be effective, they are associated with significant adverse effects, and delayed or non-durable responses.

IgG autoantibodies directed against red blood cells (RBCs) are considered to play a central role in the hemolysis and anemia observed in patients with warm autoimmune hemolytic anemia (WAIHA). SYNT001 is a humanized IgG4 mAb that blocks IgG interactions with FcRn that would be anticipated to affect the pathogenic behavior of IgG autoantibodies. Administration of SYNT001 significantly decreases total IgG levels, including a corresponding decrease in the levels of the pathogenic autoantibodies. This may lead to a decrease in the IgG coating of RBCs and the interaction of IgG-coated RBCs with FcRn in phagocytic cells, leading to decreased hemolysis in WAIHA patients with active hemolysis. Moreover, the ability of SYNT001 to reduce circulating immune complexes (CICs) and the associated innate and adaptive immune responses may allow for further sustained disease modification.

## 2.1 Study Rationale

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

## 2.2 Selection of Doses in this Study

The initial dose levels of SYNT001 for this Phase 1b/2 proof-of-concept study of 10 mg/kg and up to 30 mg/kg were selected from careful review of the safety, tolerability, and PD effect on total IgG levels after single and repeat dosing of SYNT001 in non-human primates (NHPs), as well as the safety, tolerability, and PD effect on total IgG levels after single ascending doses of SYNT001 in healthy volunteers. In addition, further consideration was given to the desired level of FcRn blockade to achieve suppression of IgG to a range that has been previously correlated with disease remission. Further, we considered the potential effects of inhibiting FcRn function as they relate to immune complex-associated innate and adaptive immunity in choosing these dose levels based upon exploratory studies of a single ascending dose of SYNT001 in healthy volunteers. From the NHP studies, single doses of SYNT001 produced a dose-dependent decrease in total IgG and a further decrease was seen with repeated weekly doses up to a maximum of 70% reduction at 100 mg/kg. This magnitude of total IgG reduction is approaching the expected maximal 90% inhibition of FcRn function based on murine studies also performed by the Sponsor and others (Nixon et al., 2015; Roopenian et al., 2003). In the recently completed Phase 1a trial with SYNT001 in healthy volunteers a single dose caused a maximum average 50% drop in total IgG with IV dosing at 30 mg/kg. Based on the NHP studies, further reductions are expected following multiple dosing. A corresponding decrease in pathogenic autoantibodies is anticipated.

A semi-mechanistic model of FcRn-IgG interactions and FcRn inhibition with SYNT001 was jointly developed by Applied BioMath and the Sponsor. The model was designed to simulate PK and PD responses to various dosing regimens of SYNT001 to inform clinical trial design. Initial simulations were able to capture both PK and PD responses to single doses of SYNT001 from a single-ascending dose study in healthy volunteers and predict multiple dose responses from ongoing studies with good fidelity. The model predicted an IgG reduction of approximately 75% by Day 33, which was determined to be acceptably close to the actual mean IgG reduction of 59% by Day 30 observed in patients. Subsequent iterations of the model have used patient data from ongoing patient studies to further calibrate dose responses. In the most recent simulations, multiple dosing scenarios have been explored, including responses to weekly, bi-weekly, and loading doses. A simulated dosing regimen consisting of three weekly loading doses of 30 mg/kg SYNT001 followed by every other week maintenance doses of 10 mg/kg SYNT001 achieved a nadir IgG reduction of approximately 78% between Days 21 and 28 and maintained an IgG reduction between approximately 50% and 68%. This level of total IgG reduction has been associated with clinical efficacy in early studies of SYNT001-treated pemphigus subjects, and represents a target for future studies in other indications. This regimen of 30 mg/kg loading doses and 10 mg/kg maintenance doses was determined to be the optimal starting regimen to achieve meaningful IgG reduction while maximizing patient safety. Future cohorts may increase the maintenance doses to 20 mg/kg SYNT001, which the model predicts will achieve greater IgG reductions between approximately 55% and 72%. Given the rigorous biological approach taken in the development of the model, simulations of dosing schedules can be considered reliable for the purpose of planning clinical trials.

Several recently completed non-clinical studies support the proposed Cohort 2 dose and dosing regimen. A recently completed 27-week dose-response good laboratory practice (GLP) toxicology study in non-human primates assessed the long-term safety, toxicology, and

toxicokinetics of weekly IV doses of SYNT001. Twenty-seven (27) once weekly 10-minute infusions of SYNT001, at doses of 5, 30, or 100 mg/kg, to cynomolgus monkeys was associated with non-adverse test article-related clinical effects and clinical pathology observations at ≥5 mg/kg. SYNT001 produced dose-dependent reduction of serum IgG levels without affecting IgA, IgM or albumin levels. The No-Observed Adverse-Effect Level (NOAEL) of SYNT001 was 100 mg/kg following 17 infusions and 30 mg/kg following 27 infusions.

As indicated above, in the recently completed Phase 1a healthy male volunteer study, single doses of SYNT001 up to and including 30 mg/kg have been well tolerated. There were no dose-limiting toxicities (DLTs), serious adverse events (SAEs), or any other safety concerns identified. No adverse events (AEs) were observed in the 1 and 3 mg/kg dose cohorts. The only moderate (Grade 2) AE observed was a single instance of headache in the 10 mg/kg cohort. Other subjects had mild (Grade 1) AEs at 10 mg/kg. In Cohort 4 (30 mg/kg), five subjects received SYNT001. All five subjects experienced AEs; all were mild (Grade 1), transient and resolved spontaneously without intervention.

A preliminary assessment of safety was conducted by SYNT001 Pemphigus Study SYNT001-103 Dose Escalation Committee (DEC). Seven subjects with pemphigus were treated with 10 mg/kg IV weekly doses over a period of 5 weeks. Overall, SYNT001 10 mg/kg IV was well tolerated. Headache (Grade 1 or 2, self-limited) was the only drug-related AE that was reported in more than one subject. Total IgG and CIC biomarkers were reduced by 59% and 50% respectively, from baseline levels following the fifth dose, returning to baseline within 1-2 months. Additionally, preliminary evidence of clinical efficacy as measured by a clinically validated scoring metric, the Pemphigus Disease Area Index, was observed across the population. The DEC approved a dose escalation of SYNT001 from 10 mg/kg IV weekly doses for 5 weeks (Cohort 1) to 30 mg/kg IV weekly doses for 5 weeks (Cohort 2).

Given these preliminary data in non-clinical toxicology species and human subjects, as well as supporting evidence from the computational model, it is anticipated that the doses and dose regimens selected for this study will be well tolerated and will demonstrate clinically relevant pharmacodynamic effects and efficacy in patients with WAIHA. For a summary of findings from the single dose clinical study in healthy subjects and further details regarding the nonclinical findings, please refer to the SYNT001 Investigators Brochure.

## 2.3 Compliance Statement

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

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

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

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

# 3. STUDY OBJECTIVES AND ENDPOINTS

| Primary Objective | Primary Endpoint |
|---|---|
| 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 AEs, treatment-emergent adverse events (TEAEs), and SAEs summarized by dose and dosing regimen, severity, and relationship to study drug |
| **Secondary Objective** | **Secondary Endpoint** |
| 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 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<br>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 |
| **Exploratory Objectives** | **Exploratory Endpoint** |
| To explore the effect of SYNT001 at different dose levels and dosing regimens on biomarkers to understand the pathophysiology of the disease | The exploration of SYNT001 mechanisms of action and effects of SYNT001 on pathophysiology summarized by dose, dosing |

| | |
|---|---|
| and the SYNT001 mechanisms of action | regimen and time point, as determined by:<br>• D-dimer<br>• Antiphospholipid antibodies (lupus anticoagulant, anti-cardiolipin antibody, anti-beta-2-GP1 antibody)<br>• Antinuclear antibody titer<br>• Anti-double-stranded deoxyribonucleic acid (dsDNA) antibody titer<br>• Quantitative Coombs assay<br>• Cold agglutinins (titer and thermal amplitude)<br>• Fc gamma R2A receptor (FCGR2A) single nucleotide polymorphisms (SNP) by genotyping<br>• Complement component 3 levels by nephelometry<br>• Presence of disease and inflammatory markers by total ribonucleic acid (RNA) sequencing<br>• 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 |

# 4. STUDY DESIGN

## 4.1 Study Sites

This study will be conducted at approximately 15 sites globally.

## 4.2 Overview of Study Design

This is a multicenter, open-label study to assess the safety, tolerability, efficacy, PK, PD, and immunogenicity of IV infusions of SYNT001 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) (Cohort 2) (Figure 1).

Subjects in both cohorts will complete the following periods of assessment: Screening, Treatment, and Follow-Up. For Cohort 1 details of the dosing schedule and assessments, see Table 2. For Cohort 2 details, see Table 3. An alternative weekly maintenance schedule of assessment for Cohort 2 is presented in APPENDIX 3, Table 10.

An overview of the study cohorts is provided in Table 4.

**Table 4. 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<br>Maintenance: 10, 20 or 30 mg/kg | 3<br>5 | Weekly<br>Every other week |
| 2 Alternative weekly schedule | Up to 12 | Loading: 10, 20 or 30 mg/kg<br>Maintenance: 10, 20 or 30 mg/kg | 3<br>10 | Weekly<br>Weekly |

Up to 8 subjects may be enrolled in Cohort 1. After 4 subjects reach Day 42, the Sponsor Medical Team will review available safety and PD data and decide the dosing regimen for Cohort 2. The maintenance dose frequency may be increased to weekly (Cohort 2 alternative weekly maintenance schedule). Dosing regimen decisions for Cohort 2 will be communicated to the sites prior to Day 0 dosing.

The Sponsor Medical Team will consist of at least the Medical Monitor and the Sponsor Medical Lead. The Sponsor Medical Team may request that Investigators, other experts, or members within their organization participate in the review.

Subjects in Cohorts 1 and 2 will be enrolled at staggered intervals to facilitate adequate safety evaluation before dosing of subsequent subjects may proceed.

At 24-hour and 7-day intervals described below, available safety data (including, but not limited to, DLTs, AEs, TEAEs, SAEs), and PD (including, but not limited to, total IgG levels) will be reviewed.

**Safety Review of 24-hour Data for Cohorts 1 and 2, Subject 1**

- The first 2 subjects will be dosed at least 24 hours apart. A DEC 24-hour safety data review for the first subject in Cohort 1 will be performed to ensure that there are no overt safety concerns before dosing the second subject. The Sponsor Medical Team will conduct the 24-hour safety data review for the first subject in Cohort 2.

**Safety Review of 7-day Data for Cohorts 1 and 2, Subjects 1 and 2**

- The 7-day safety data for the first 2 subjects in Cohort 1 will be performed by the DEC prior to dosing the remaining subjects in the cohort.

- The 7-day safety data for the first 2 subjects in Cohort 2 will be performed by the Sponsor Medical Team prior to dosing the remaining subjects in the cohort.

The 24-hour and 7-day reviews will consider seriousness and severity of AEs/TEAEs/SAEs and relatedness to study drug, vital sign assessments, physical examinations, and clinical laboratory testing.

## 4.3 Randomization and Blinding

This is an open-label study.

## 4.4 Duration of Subject Participation

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

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

# 5. STUDY POPULATION

## 5.1 Target Population

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.

## 5.2 Inclusion Criteria

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

1. Willing and able to read, understand and sign an informed consent form.
2. Male or female ≥18 years of age at the time of screening.
3. Confirmed diagnosis by enrolling physician of WAIHA, including positive direct Coombs test.
4. Hemoglobin <11 g/dL.
5. Evidence of active hemolysis including any one of the below:
   a. LDH >upper limit of normal (ULN) or
   b. Haptoglobin <lower limit of normal (LLN) or
   c. Indirect bilirubin >ULN.
6. Other treatments for WAIHA:
   a. If treated with rituximab or other anti-CD20 mAb, last dose >3 months prior to screening (a dose is defined as ≥10% of the intended dose).
   b. If being treated with other immunosuppressants (ie, azathioprine, mycophenolate mofetil, methotrexate, cyclosporine, tacrolimus, sirolimus, or low-dose oral cyclophosphamide [≤100 mg/day]), dose must be stable (<25% change in dose) for the 4 weeks prior to screening.
   c. If being treated with corticosteroids, dose must be ≤1mg/kg/day of prednisone or equivalent, and the dose may not be increased by more than 50% in the 2 weeks prior to screening.
   d. No pulse corticosteroids are allowed in the 2 weeks prior to screening.
7. Treatment of chronic lymphocyte leukemia (CLL) or non-Hodgkin lymphoma (NHL) must be:
   a. FDA-approved for oral treatment,
      and
   b. Stable (<10% change in dose) for 6 weeks prior to screening; Bruton's tyrosine kinase inhibitor dose must be stable (<10% change in dose) for 8 weeks prior to screening.
8. Body mass index (BMI) >18.5 kg/$m^2$.
9. Has a negative pregnancy test (for women of childbearing potential) documented prior to the first dose of study drug.
10. Females of childbearing potential must agree to be abstinent or else use any two of the following medically acceptable forms of contraception (<1% per year failure rate) from the screening period through the final study visit: oral contraceptive, condom with or without spermicidal jelly, diaphragm or cervical cap with spermicidal jelly, or intra-uterine device (IUD). A female whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception.

11. Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal for at least 12 months do not require contraception during the study.
12. Males with female partners of childbearing potential, including males who are surgically sterile (post vasectomy), must agree to be abstinent or else use a medically acceptable form of contraception from the screening period through the final study visit.

## 5.3 Exclusion Criteria

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

1. Subject unable or unwilling to comply with the protocol.
2. Active non-hematologic malignancy or history of non-hematologic malignancy in the 3 years prior to screening (exclusive of non-melanoma skin cancer and cervical cancer in situ).
3. Karnofsky Performance Scale ≤50.
4. Estimated glomerular filtration rate (eGFR) <45 mL/minute/1.73m$^2$.
5. Platelet count <30 ×10$^9$/L.
6. Corrected reticulocyte count <2% (using the following calculation; (% reticulocyte x % hematocrit) / normal hematocrit [45%]).
7. Positive for human immunodeficiency virus (HIV) or hepatitis C antibody.
8. Positive for hepatitis B surface antigen.
9. Splenectomy within 3 months of screening.
10. Any T-cell or NK-cell NHL, and any moderate- or high-grade B-cell lymphoma, including Burkitt lymphoma, lymphoblastic B-cell lymphoma, diffuse large B-cell lymphoma, mantle cell lymphoma, or small non-cleaved cell non-Burkitt lymphoma.
11. Received any cytotoxic (other than azathioprine, chlorambucil, low-dose methotrexate, or low-dose oral cyclophosphamide [≤100 mg/day]), or any non-anti-CD20 mAb therapy in the 3 months prior to screening.
12. Any exposure to an investigational drug or device within 30 days prior to screening.
13. IVIG treatment within 30 days of screening.
14. Plasmapheresis or immunoadsorption within 30 days of screening.
15. Cellular therapy, including chimeric antigen receptor and T-cell (CAR-T), at any time prior to screening.
16. Use of any immunosuppressive drugs within 3 months of screening, not including those allowed by the inclusion criteria.
17. Active infection or history of recurrent infections.
18. Serum total IgG <600 mg/dL.
19. Subject has any current medical condition that, in the opinion of the Investigator, may compromise their safety or compliance, preclude successful conduct of the study, or interfere with interpretation of the results (eg, a significant pre-existing illness or other major comorbidity that the Investigator considers may confound the interpretation of the study results).
20. Any vaccination within 2 weeks of screening.

# 6. STUDY PROCEDURES

## 6.1 Informed Consent

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

## 6.2 Demographics and Medical History

Demographics (age, gender, race and ethnicity) and medical history will be obtained from the subject and recorded on the source document and 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.

## 6.3 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.

## 6.4 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. See Appendix 2.

## 6.5 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.

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; and 30 minutes, 1 hour and 2 hours following completion of the infusion. Abnormalities in vital sign measurements will be graded in severity per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) scale Version 4.03.

**Table 5. Timing window allowances for PK/PD sampling, ECG, and vital sign measurements at dosing visits**

| **Time Point** | **Tolerance Window** | |
|---|---|---|
| | **Cohort 1** | **Cohort 2** |
| **Pharmacokinetic Sampling** | | |
| 0 hour | −240 minutes to 0 hour | −240 minutes to 0 hour |
| 5 minutes post end-of-infusion | ±5 minutes | ±5 minutes |
| 1 hour post end-of-infusion | N/A | ±15 minutes |
| 2 hours post end-of-infusion | ±15 minutes | ±15 minutes |
| 4 and 6 hours post end-of-infusion | ±15 minutes | N/A |
| 24 hours 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).

## 6.6 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 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 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.

## 6.7 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 (for screening purposes, retest can be performed using established methods by the local laboratory). Clinical safety laboratory panels are listed in Table 6. Blood and urine for hematology, serum chemistry, and urinalysis will be prepared using standard procedures. Results will be provided to the Investigator. Aliquots from the PK, biomarker and ADA samples may be retained as back-up for additional testing as necessary. Subjects will be in a seated or supine position during blood collection.

**Table 6. Clinical Safety Laboratory Panels**

| Hematology | Serum Chemistry | Urinalysis |
|---|---|---|
| • CBC with differential and blood smear | • Albumin<br>• Alkaline phosphatase<br>• ALT | • Appearance<br>• Color<br>• pH |

**Table 6. Clinical Safety Laboratory Panels**

| Hematology | Serum Chemistry | Urinalysis |
|---|---|---|
| | • AST<br>• BUN<br>• C-Reactive Protein<br>• Calcium<br>• Carbon dioxide<br>• Chloride<br>• Creatinine<br>• Creatine Phosphokinase<br>• Glucose<br>• LDH<br>• Phosphorus<br>• Potassium<br>• Sodium<br>• Total and direct bilirubin<br>• Total protein<br>• Uric acid | • Specific gravity<br>• Ketones<br>• Protein<br>• Glucose<br>• Nitrite<br>• Urobilinogen<br>• Blood/hemoglobin<br>• Leukocyte esterase<br>• Bilirubin<br>• Microscopic examination of sediment: only if the results of the urinalysis dipstick evaluation are positive for blood/hemoglobin |

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. If laboratory values constitute part of an event that meets criteria defining it as serious, the event (and associated laboratory values) must be reported as an SAE (see Section 10.3.1).

### 6.7.1 Pregnancy Testing

Pregnancy testing will be performed for women of childbearing potential. Urine or serum test is acceptable; however, positive urine tests must be confirmed with serum testing.

### 6.7.2 Virology

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

### 6.7.3 Serum Tetanus Antibody and Varicella-Zoster Virus Antibody Testing

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

### 6.7.4 Pharmacokinetics (PK) Sampling

The following PK parameters will be studied in Cohort 1: $t_{1/2}$, $C_{max}$, $T_{max}$, $AUC_{0-24}$, and $AUC_{0-\infty}$. For all successive cohorts, the PK parameters studied will be maximum serum concentration of SYNT001 and the associated $T_{max}$.

See Table 5 for timing window allowances with respect to PK samples. Detailed instructions for sample collection and preparation will be provided in a separate laboratory manual.

### 6.7.5 Pharmacodynamic Sampling

PD samples will be collected for analyses throughout the study. 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 7.

## Table 7. Pharmacodynamic Assessments

| Parameter | Collection Time Points | |
|---|---|---|
| | **Cohort 1** | **Cohort 2[a]** |
| Immunoglobulins:<br>IgG<br>IgG subtypes (IgG1-4)<br>IgA<br>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<br>Hematocrit<br>Hemoglobin<br>Haptoglobin<br>Platelet count<br>Reticulocyte count<br>Lactate dehydrogenase (LDH)<br>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<br>(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<br>Antiphospholipid antibodies<br>Lupus anticoagulant<br>Anti-cardiolipin antibody<br>Anti-beta-2-GP1 antibody<br>Antinuclear antibody (ANA) titer<br>Anti-dsDNA antibody titer<br>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;<br>• $CD3^+CD4^+$ T<br>• $CD3^+CD8^+$ T<br>• monocytes<br>• NK cells<br>• 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. See Appendix 3 for the corresponding visit schedule.**

See Table 5 for timing window allowances with respect to measurement collection Immunoglobulins.

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

### 6.7.6 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.

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

### 6.7.7 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).

### 6.7.8 Direct Antiglobulin (Coombs) Test (DAT)

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.

### 6.7.9 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.

## 6.8 Study Drug Administration

Up to 20 subjects are planned; up to 8 subjects in Cohort 1 and up to 12 subjects in Cohort 2.

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.

Investigators may adjust the duration of the infusion if needed to increase tolerability. Prepared SYNT001 should be used within 4 hours as described in the pharmacy manual. Full information on infusion preparation and administration refer to pharmacy manual.

See Section 9 for details of study drug.

## 6.9 Adverse Event Assessments

Information regarding the occurrence of AEs will be collected from the time the subject signs the informed consent form and continuing through the last study visit. Findings at screening and Day 0 (pre-dose) will be recorded as medical history. Any known untoward event that occurs beyond the AE reporting period that the Investigator assesses as related to study drug also should be reported as an AE. Clinical AEs will be graded using the NCI CTCAE, Version 4.03 (Appendix 1).

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

See Section 10 for more information.

## 6.10 Prior and Concomitant Medications

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.

In cases in which concomitant medications are used, details to be recorded include the following: medication name, start date and time, stop date and time, dose, route, frequency, and reason for use. The concomitant medication names are to be coded using the World Health Organization (WHO) Drug Dictionary (WHO-DD March 2013, Type B2 or later) and classified by anatomical therapeutic chemical (ATC) categories.

**Permitted Medications**

The following concomitant medications and treatment for co-existing conditions, including those for WAIHA, are permitted if not listed as prohibited:

1. Concomitant treatment that is medically indicated for any AEs the subject experiences during the study.
2. Medication for potential infusion-related reactions (IRRs), including post-infusion headache: The Investigator may recommend prophylactic use of acetaminophen, IV hydration, diphenhydramine, or histamine$_2$ blockers (eg, ranitidine, famotidine).
3. Stable regimen of the following systemic immunosuppressants: azathioprine, mycophenolate mofetil, low-dose methotrexate, cyclosporine, tacrolimus, sirolimus, corticosteroids, or low-dose oral cyclophosphamide (≤100 mg/day).

**Prohibited Medications**

The following treatments are prohibited during the study unless specified above as permitted:

1. Rituximab or other anti-CD20 antibody
2. Monoclonal antibodies other than study drug.
3. Any immunosuppressive drugs apart from those that are listed as permitted.
4. Any cytotoxic agent other than azathioprine, chlorambucil, low-dose methotrexate, or low-dose oral cyclophosphamide (≤100 mg/day).
5. IV corticosteroids prior to infusion of study drug (except in subjects who received corticosteroids for treatment of a prior infusion reaction to SYNT001).
6. Any investigational drug or device.
7. Vaccinations within 2 weeks of screening through 28 days following final dose of study drug.

**WAIHA Co-medication**

Subjects receiving WAIHA treatment at enrollment, should remain on a stable treatment regimen throughout dosing and for the 14 days after the last dose of SYNT001.

**Corticosteroids**

Before enrollment

The dose of corticosteroids taken for WAIHA or any other condition prior to screening must be at a dose ≤1 mg/kg and the dose level must have not increased in dose level by more than 50% in the 2 weeks prior to screening. No pulse dosing of steroids is permitted in the 2 weeks prior to screening.

From screening until 2 weeks after the last dose of SYNT001

The dose of corticosteroids taken for WAIHA or any other condition should remain stable (<10% change in dose level) from screening until 2 weeks after the last dose of SYNT001. Corticosteroids should neither be started nor discontinued during this period with the exception of subjects who experience an IRR that requires corticosteroids as part of the management of the

IRR. Such subjects may receive corticosteroids prophylactically prior to subsequent SYNT001 infusions at the discretion of the Investigator.

From 2 weeks after the last dose of SYNT001 until end of study participation

At the discretion of the Investigator, but only after at least 2 weeks beyond the last dose of SYNT001, a slow corticosteroid taper may be started as per the following suggested schedule:

- If on >30 mg of prednisone per day, decrease by no more than 10 mg every two weeks until a final dose.

If per the Investigator's judgement, the subject would benefit from a change to the WAIHA treatment beyond the allowed steroid taper, this will be considered on a case-by-case basis in consultation with the Sponsor.

# 7. STUDY ASSESSMENTS

## 7.1 Cohort 1 Assessments

### 7.1.1 Screening Period: Day −14 to Day −1

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

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

- Informed consent (Section 6.1)
- Medical history and demographic data (Section 6.2)
- Review inclusion and exclusion criteria (Section 5.2, Section 5.3)
- Complete physical examination, including height and weight (Section 6.3)
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Karnofsky Performance Scale (Section 6.4)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- Pregnancy test (Section 6.7)
- Hepatitis and HIV antibody screen (Section 6.7)
- 12-lead ECG (to be obtained in triplicate after 5 minutes of rest in the supine position) (Section 6.6)
- PD sample collection (Section 6.7)
    - IgG, IgG subtypes (IgG1-4), IgA, IgM
    - Haptoglobin
    - Direct Coombs test
- Concomitant medication assessment (Section 6.10)
- AE assessment (Section 6.9)

### 7.1.2 Enrollment and First Treatment: Day 0

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

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

- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- Pregnancy test (Section 6.7)
- Serum tetanus antibody and VZV antibody (Section 6.7)
- PK baseline sample collection (collected just prior to the start of the study drug infusion) (Section 6.7)
- Immunogenicity sample collection (collected just prior to the start of study drug infusion) (Section 6.7)
- PD sample collection (collected just prior to the start of the study drug infusion) (Section 6.7)
    - IgG, IgG subtypes (IgG1-4), IgA, IgM and CIC
    - Haptoglobin
    - Direct Coombs test
    - D-dimer
    - Antiphospholipid antibodies (lupus anticoagulant, anti-cardiolipin, and anti-beta-2-GP1 antibodies)
    - ANA and anti-dsDNA antibody titers
    - C3
    - Cold agglutinins (titer and thermal amplitude)
    - Quantitative Coombs assay
    - Exploratory biomarkers (*FCGR2A* SNP via buccal swab, RNA sequencing [RNAseq], urine IgG)
    - Immune phenotyping by flow cytometry for measurement of $CD3^+CD4^+$ T, $CD3^+CD8^+$ T, monocytes, NK cells and B cells
- Concomitant medication assessment (Section 6.10)
- AE assessment (Section 6.9)

**After the preceding procedures and assessments are completed:**

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

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

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

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

### 7.1.3 Follow-up: Day 1

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

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

### 7.1.4 Follow-up: Day 2

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

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

### 7.1.5 Follow-up: Day 5

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

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

- PK sampling (record collection date and time) (Section 6.7)
- Concomitant medication assessment (Section 6.10)
- AE assessment (Section 6.9)

### 7.1.6 Treatment Day 7 (Dose 2)

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

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

**After the preceding procedures and assessments are completed:**

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

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

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

### 7.1.7 Dose 2 Follow-up: Day 12

On Day 12 (± 6 hours), subjects may return to the clinic or be visited by an at-home nurse, and the following procedures are to be performed:

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

### 7.1.8 Treatment Day 14 (Dose 3)

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

- Complete physical examination (Section 6.3)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature); to be measured immediately prior to the infusion (Section 6.5)
- Pulse oximetry (to be measured immediately prior to the infusion) (Section 6.5)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- Immunogenicity sample collection (collected just prior to the start of study drug infusion) (Section 6.7)
- PD sample collection (collected just prior to the start of the study drug infusion) (Section 6.7)
    - IgG, IgG subtypes (IgG1-4), IgA, IgM and CIC
    - Haptoglobin
    - Direct Coombs test
    - D-dimer
    - Antiphospholipid antibodies (lupus anticoagulant, anti-cardiolipin, and anti-beta-2-GP1 antibodies)
    - ANA and anti-dsDNA antibody titers
    - C3
    - Quantitative Coombs assay
    - Exploratory biomarkers (RNAseq, urine IgG)
- Concomitant medication assessment (Section 6.10)
- AE assessment (Section 6.9)

**After the preceding procedures and assessments are completed:**

- Study drug administration (record date and time of dose of study drug) (Section 9)

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

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

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

### 7.1.9 Dose 3 Follow-up: Day 19

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

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

### 7.1.10 Treatment Day 21 (Dose 4)

On Day 21 (± 6 hours) subjects will return to the clinic and the following procedures are to be performed prior to study drug infusion:

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

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

**After the preceding procedures and assessments are completed:**

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

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

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

### 7.1.11 Treatment Day 28 (Dose 5)

On Day 28 (± 6 hours) subjects will return to the clinic and the following procedures are to be performed prior to study drug infusion:

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

  - Immune phenotyping by flow cytometry for measurement of $CD3^+CD4^+$ T, $CD3^+CD8^+$ T, monocytes, NK cells and B cells
- Concomitant medication assessment (Section 6.10)
- AE assessment (Section 6.9)

**After the preceding procedures and assessments are completed:**

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

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

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

### 7.1.12 Follow-up: Day 29

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

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

### 7.1.13 Follow-up: Day 30

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

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

### 7.1.14 Follow-up: Day 33

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

- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature): abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- PD sample collection (Section 6.7)
    - IgG, IgG subtypes (IgG1-4), IgA, IgM and CIC
    - Haptoglobin
    - Direct Coombs test
    - D-dimer
    - Antiphospholipid antibodies (lupus anticoagulant, anti-cardiolipin, and anti-beta-2-GP1 antibodies)
    - ANA and anti-dsDNA antibody titers
    - C3
    - Cold agglutinins (titer and thermal amplitude)
    - Quantitative Coombs assay
    - Exploratory biomarkers (RNAseq, urine IgG)
- PK sampling (record collection date and time) (Section 6.7)
- Concomitant medication assessment (Section 6.10)
- AE assessment (Section 6.9)

### 7.1.15 Follow-up: Day 42

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

- Complete physical exam (Section 6.3)

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

### 7.1.16 Follow-up: Day 56

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

- Complete physical examination (Section 6.3)
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature): abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- Pregnancy test (Section 6.7)
- 12-Lead ECG (to be obtained in triplicate at 5 minutes after the completion of study drug infusion (Section 6.6)
- Serum tetanus antibody and VZV antibody; testing at Day 56 will not be done for any subject whose baseline titer is below the level of detection. See Section 6.7.3 for additional information.
- Immunogenicity sample collection (Section 6.7)
- PD sample collection (Section 6.7)
    - IgG, IgG subtypes (IgG1-4), IgA, IgM and CIC
    - Haptoglobin
    - Direct Coombs test
    - D-dimer
    - Antiphospholipid antibodies (lupus anticoagulant, anti-cardiolipin, and anti-beta-2-GP1 antibodies)
    - ANA and anti-dsDNA antibody titers
    - C3
    - Cold agglutinins (titer and thermal amplitude)
    - Quantitative Coombs assay
    - Exploratory biomarkers (RNAseq, urine IgG)
    - Immune phenotyping by flow cytometry for measurement of $CD3^+CD4^+$ T, $CD3^+CD8^+$ T, monocytes, NK cells and B cells
- Concomitant medication assessment (Section 6.10)
- AE assessment (Section 6.9)

### 7.1.17 Follow-up: Day 84

On Day 84 (± 5 days), subjects are to return to the clinic and the following procedures are to be performed:

- Complete physical examination (Section 6.3)
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature): abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- Serum tetanus antibody and VZV antibody if required. See Section 6.7.3 for additional information.
- Immunogenicity sample collection (Section 6.7)
- PD sample collection (Section 6.7)
    - IgG, IgG subtypes (IgG1-4), IgA, IgM and CIC
    - Haptoglobin
    - Direct Coombs test
    - D-dimer
    - Antiphospholipid antibodies (lupus anticoagulant, anti-cardiolipin, and anti-beta-2-GP1 antibodies)
    - ANA and anti-dsDNA antibody titers
    - C3
    - Cold agglutinins (titer and thermal amplitude)
    - Exploratory biomarkers (RNAseq, urine IgG)
- Concomitant medication assessment (Section 6.10)
- AE assessment (Section 6.9)

### 7.1.18 Follow-up: Day 112 (End of Study) or Early Termination Visit

On Day 112 (± 5 days), subjects are to return to the clinic and the following procedures are to be performed:

- Complete physical examination (Section 6.3)
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature): abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- Pregnancy test (Section 6.7)
- Serum tetanus antibody and VZV antibody; testing if required. See Section 6.7.3 for additional information.
- Immunogenicity sample collection (Section 6.7)
- PD sample collection (Section 6.7)
    - IgG, IgG subtypes (IgG1-4), IgA, IgM and CIC
    - Haptoglobin

  - Direct Coombs test
  - D-dimer
  - Antiphospholipid antibodies (lupus anticoagulant, anti-cardiolipin, and anti-beta-2-GP1 antibodies)
  - ANA and anti-dsDNA antibody titers
  - C3
  - Cold agglutinins (titer and thermal amplitude)
  - Exploratory biomarkers (RNAseq, urine IgG)
- Concomitant medication assessment (Section 6.10)
- AE assessment (Section 6.9)

## 7.2 Cohort 2 Assessments

### 7.2.1 Screening Period: Day −28 to Day −1

Informed consent must be obtained before any study-specific samples are taken or study-specific tests or evaluations are conducted. The following assessments at the screening visit are to occur within 28 days before dosing. Study eligibility will be based on satisfying all the study inclusion and exclusion criteria.

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

- Informed consent (Section 6.1)
- Medical history and demographic data (Section 6.2)
- Review inclusion and exclusion criteria (Section 5.2, Section 5.3)
- Complete physical examination, including height and weight (Section 6.3)
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature); abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Karnofsky Performance Scale (Section 6.4)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- Pregnancy test (Section 6.7)
- Hepatitis and HIV antibody screen (Section 6.7)
- 12-lead ECG (to be obtained in triplicate after 5 minutes of rest in the supine position) (Section 6.6)
- Immunogenicity sample collection (collected just prior to the start of study drug infusion) (Section 6.7)
- PD sample collection (Section 6.7)
  - IgG, IgG subtypes (IgG1-4), IgA, IgM
  - Haptoglobin
  - Direct Coombs test
- Concomitant medication assessment (Section 6.10)
- AE assessment (Section 6.9)

### 7.2.2 Enrollment and First Treatment: Day 0

Study Day 0 is defined as the date the subject is administered their first dose of study drug. Subjects should be encouraged drink two 8-ounce glasses of water prior to dosing. On Day 0, subjects will be asked to come to the clinic and the following procedures will be performed prior to the first dose of study drug:

- Complete physical examination (Section 6.3)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature); to be measured immediately prior to the infusion (Section 6.5)
- Pulse oximetry (to be measured immediately prior to the infusion) (Section 6.5)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- Pregnancy test (Section 6.7)
- Serum tetanus antibody and VZV antibody (Section 6.7)
- PK baseline sample collection (collected just prior to the start of the study drug infusion) (Section 6.7)
- Immunogenicity sample collection (collected just prior to the start of study drug infusion) (Section 6.7)
- PD sample collection (collected just prior to the start of the study drug infusion) (Section 6.7)
    - IgG, IgG subtypes (IgG1-4), IgA, IgM and CIC
    - Haptoglobin
    - Direct Coombs test
    - 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.
    - Cold agglutinins (titer and thermal amplitude)
    - Quantitative Coombs assay
    - Exploratory biomarkers (*FCGR2A* SNP via buccal swab, RNAseq)
    - Immune phenotyping by flow cytometry for measurement of $CD3^+CD4^+$ T, $CD3^+CD8^+$ T, monocytes, NK cells and B cells
- Concomitant medication assessment (Section 6.10)
- AE assessment (Section 6.9)

**After the preceding procedures and assessments are completed:**

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

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

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

### 7.2.3 Loading Doses 2 and 3 (Cohort 2 weekly Day 7 and 14 [±1 day])

Subjects will return to the clinic for loading doses 2 and 3. Subjects should be encouraged to drink two 8-ounce glasses of water prior to dosing. The following procedures are to be performed prior to study drug infusion:

- Complete physical examination (Section 6.3)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature); to be measured immediately prior to the infusion (Section 6.5)
- Pulse oximetry (to be measured immediately prior to the infusion) (Section 6.5)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- Immunogenicity sample collection (collected just prior to the start of study drug infusion) (Section 6.7)
- PK sample collection (collected just prior to the start of the study drug infusion) (Section 6.7)
- PD sample collection (collected just prior to the start of the study drug infusion) (Section 6.7)
    - IgG, IgG subtypes (IgG1-4), IgA, IgM and CIC
    - Haptoglobin
    - Day 14 ONLY: Direct Coombs test
    - Day 14 ONLY: Quantitative Coombs assay
- Concomitant medication assessment (Section 6.10)
- AE assessment (Section 6.9)

**After the preceding procedures and assessments are completed:**

- Study drug administration (record date and time of dose of study drug) (Section 9)

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

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

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature): 30 minutes, 1 hour, and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Pulse oximetry: 30 minutes, 1 hour, and 2 hours following completion of the infusion (Section 6.5)
- Day 14 ONLY: 12 Lead ECG (to be obtained in triplicate at 5 minutes after the completion of study drug infusion (Section 6.6)
- PK sample collection at 5 minutes, 1 and 2 hours after the completion of study drug infusion; record collection date and time for each PK sample (Section 6.7)
- Concomitant medication assessment (Section 6.10)
- AE assessment (Section 6.9)

### 7.2.4 Maintenance Doses (Cohort 2 every other Week Day 28, 42, 56, and 70 [± 3 days])

Subjects will return to the clinic for maintenance doses in Cohort 2 every other week dosing on Day 28, 42, 56, and 70. Subjects should be encouraged drink two 8-ounce glasses of water prior to dosing. The following procedures are to be performed prior to study drug infusion:

- Complete physical examination (Section 6.3)
- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature); to be measured immediately prior to the infusion (Section 6.5)
- Pulse oximetry (to be measured immediately prior to the infusion) (Section 6.5)
- Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- Day 28 ONLY: Pregnancy test (Section 6.7)
- Day 28 ONLY: Serum tetanus antibody and VZV antibody (Section 6.7)
- Immunogenicity sample collection (collected just prior to the start of study drug infusion) (Section 6.7)
- Day 28 ONLY: PK sample collection (collected just prior to the start of the study drug infusion) (Section 6.7)
- PD sample collection (collected just prior to the start of the study drug infusion) (Section 6.7)
    - IgG, IgG subtypes (IgG1-4), IgA, IgM and CIC

  - Haptoglobin
  - Day 28 ONLY: Direct Coombs test
  - Day 28 ONLY: 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.
  - Day 28 ONLY: Cold agglutinins (titer and thermal amplitude)
  - Day 28 ONLY: Exploratory biomarkers (RNA seq)
  - Day 28 ONLY: Quantitative Coombs assay
  - Day 28 ONLY: Immune phenotyping by flow cytometry for measurement of $CD3^+CD4^+$ T, $CD3^+CD8^+$ T, monocytes, NK cells and B cells
- Concomitant medication assessment (Section 6.10)
- AE assessment (Section 6.9)

**After the preceding procedures and assessments are completed:**

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

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

- Vital sign measurements (sitting blood pressure, heart rate, respiratory rate, oral temperature): 30 minutes, 1 hour, and 2 hours following completion of the infusion; abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Pulse oximetry: 30 minutes, 1 hour, and 2 hours following completion of the infusion (Section 6.5)
- Day 28 ONLY: PK sample collection at 5 minutes, 1 and 2 hours after the completion of study drug infusion; record collection date and time for each PK sample (Section 6.7)
- Day 28 ONLY: 12 Lead ECG (to be obtained in triplicate at 5 minutes after the completion of study drug infusion) (Section 6.6)
- Concomitant medication assessment (Section 6.10)
- AE assessment (Section 6.9)

### 7.2.5 Final Maintenance Dose Visit (Cohort 2 Day 84)

Subjects will return to the clinic for the final maintenance dose on Day 84 ±3 days. Subjects should be encouraged drink two 8-ounce glasses of water prior to dosing. The following procedures are to be performed prior to study drug infusion:

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

**After the preceding procedures and assessments are completed:**

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

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

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

### 7.2.6 Follow-up: Day 91, 112, and 140 (± 5 days) (Day 91 is Early Termination [ET] Visit and Day 140 is End of Study [EOS] Visit)

On Day 91, 112, and Day 140, subjects are to return to the clinic and the following procedures are to be performed.

*Note: If a subject prematurely discontinues study drug, the subject should be encouraged to attend, at a minimum, the early termination (ET) visit (Day 91), and subjects will also be encouraged to attend the remaining study visits (Days 112, and 140).*

*Subjects who prematurely discontinue from the study during follow up should attend the end of study (EOS) visit on Day 140.*

- Day 91 and 140 ONLY: Complete physical examination (Section 6.3)
- Vital sign measurements (after 5 minutes of rest; sitting blood pressure, heart rate, respiratory rate, oral temperature): abnormal results to be repeated after 5 minutes of rest (Section 6.5)
- Day 91 and 140 ONLY: Clinical safety laboratory tests (hematology, serum chemistry panel, urinalysis) (Section 6.7)
- Day 91 and 140 ONLY: Pregnancy test (Section 6.7)
- Day 91 and 140 ONLY: 12 Lead ECG (Section 6.6)
- Day 91 and 140 ONLY: Serum tetanus antibody and VZV antibody See Section 6.7.3 for additional information.
- Immunogenicity sample collection (Section 6.7)
- PD sample collection (Section 6.7)
    - IgG, IgG subtypes (IgG1-4), IgA, IgM and CIC
    - Haptoglobin
    - Day 91 and 140 ONLY: Direct Coombs test
    - Day 91 ONLY: 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.
    - Day 91 and 140 ONLY: Cold agglutinins (titer and thermal amplitude)
    - Day 91 ONLY: Exploratory biomarkers (RNAseq)
    - Day 91 ONLY: Immune phenotyping by flow cytometry for measurement of $CD3^+CD4^+$ T, $CD3^+CD8^+$ T, monocytes, NK cells and B cells
    - Day 91 ONLY: Quantitative Coombs assay
- Concomitant medication assessment (Section 6.10)
- AE assessment (Section 6.9)

# 8. STUDY RULES

## 8.1 Subject Withdrawal

Every reasonable effort will be made to keep the subject in the study; however, if a subject withdraws from the study, the Investigator should complete and report the reasons for withdrawal as thoroughly as possible. The reason(s) for termination must be clearly documented on the appropriate page of the eCRF.

Subjects who have received at least one SYNT001 dose and withdraws or prematurely discontinue study drug should be encouraged to attend, at a minimum, the early termination (ET) visit (Day 112 for Cohort 1 or Day 91 for Cohort 2). Subjects in Cohort 2 will also be encouraged to attend the remaining follow up visits on Days 112, and 140.

If the subject fails to return for these assessments for unknown reasons, every effort (eg, telephone, email, and letter) should be made to contact them.

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

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

## 8.2 Subject Replacement

Enrolled subjects withdrawn for a reason other than an AE may be replaced.

## 8.3 Study Discontinuation

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

- The incidence or severity of AEs in this or other related studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory
- Drug supply issues

- Excessive subject self-withdrawal
- Significant protocol violations (eg, violation of eligibility criteria, dosing errors, missing data for study endpoint analysis)

## 8.4 Lost to Follow up

All reasonable effort should be made to contact any subject lost to follow-up during the study to complete assessments and retrieve any outstanding data. If the subject is unreachable after three good faith attempts, **at a minimum, the Investigator should follow up with a registered letter requesting contact** so safety data may be collected, recorded, and reported (if necessary).

## 8.5 Stopping Rule

### 8.5.1 Dose-Escalation Stopping Rule

Up to 8 subjects may be enrolled in Cohort 1. After 4 subjects reach Day 42, the Sponsor Medical Team will review available safety and PD data and will decide the dosing regimen for Cohort 2.

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

If 2 or more subjects at any time in any cohort have Grade 3 AEs that are determined to be clinically significant and considered to be related to study drug, dosing will be halted within that cohort and dose-escalation to a higher dose will not occur. If the dose-escalation stopping rule is met during Cohort 1 (10 mg/kg) all safety data and all available PD will be reviewed and the cohort may resume (if applicable) or a new cohort may be added at a dose at least 50% lower than the 10 mg/kg dose. If the stopping rule is not met in Cohort 1, dose-escalation may proceed up to a maximum of 30 mg/kg.

### 8.5.2 Study Stopping Rule

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

### 8.5.3 Individual Stopping Rule

Dosing for any individual subject will be discontinued (ie, further treatment with the study drug will not be given) if the subject experiences any study drug-related SAE or any study drug-related non-serious AE that, in the judgement of the Investigator (following consultation with Medical Monitor, if desired) suggests that it could be unsafe to administer further study drug to that subject.

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

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

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

Additionally, a subject will be discontinued from further treatment with study drug, at the discretion of the Investigator with consultation with the Medical Monitor, if they require a significant increase in doses of anti-WAIHA medications for the management of WAIHA.

If dosing with study drug is stopped because of an AE/SAE, or because of significant increase in doses of anti-WAIHA medications, or any other reason for prematurely discontinuation of study drug during the treatment period, the subject should be encouraged to attend, at a minimum, the ET visit (Day 112 for Cohort 1 or Day 91 for Cohort 2). Subjects in Cohort 2 will also be encouraged to attend the remaining follow up visits on Days 112, and 140.

# 9. STUDY DRUG

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

## 9.1 SYNT001

SYNT001 is provided in vials containing 5 mL SYNT001 (extractable volume) at a nominal concentration of 50 mg/mL. The product is supplied as a liquid at pH 6.5 ± 0.5. SYNT001 is diluted in dextrose 5% in water (D5W) to prepare the solution for infusion. SYNT001 will be infused via IV in 250 mL over 1 hour ±15 minutes using a 0.2-micron, inline filter.

Investigators may adjust the duration of the infusion if needed to increase tolerability. Prepared SYNT001 should be used within 4 hours as described in the pharmacy manual. For detailed information regarding SYNT001 preparation and administration, refer to the Pharmacy Manual.

## 9.2 Dose Requirements

The specification for host cell deoxyribonucleic acid (DNA) in SYNT001 is <2 pg/mg, the limit of quantitation of the assay. To comply with regulatory guidelines, which specify a maximum level of 10 ng host cell DNA per dose, dosing per subject is limited to 5000 mg SYNT001. For example, a subject with a body weight of 166 kg and enrolled in the ≤30 mg/kg dose cohort will receive ≤4960 mg SYNT001 per dose. If a subject's body weight extrapolates to an expected dose ≥5000 mg SYNT001, the dose will be capped to ensure the 5000 mg SYNT001 per dose limit is not exceeded.

## 9.3 Cohort Dosing

Enrolled subjects will receive SYNT001 according to their dose-cohort assignment:

**Cohort 1:** 10 mg/kg weekly x 5 doses

**Cohort 2:** 10, 20 or 30 mg/kg weekly x 3 doses (Loading), followed by 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).

Up to 8 subjects may be enrolled in Cohort 1. After 4 subjects reach Day 42, the Sponsor Medical Team will review available safety and PD data and will decide the dosing regimen for Cohort 2.

## 9.4 Handling and Storage of SYNT001

SYNT001 will be supplied by the Sponsor and must be stored refrigerated (2ºC to 8ºC/36ºF to 46ºF) in the carton and protected from light, in a securely locked area, accessible to authorized persons only, until needed for dose preparation.

## 9.5 Study Drug Accountability

The Investigator (or designee) is responsible for maintaining accurate accountability records of the study drug throughout the clinical study. Qualified site personnel will inventory the investigational product received and will maintain records of disposition of the drug, including dates, quantity and use. All study drug received at the site must be accounted for on an accountability log provided by the Sponsor. All dispensing and accountability records will be available for Sponsor review. Study drug accountability will be verified during on-site monitoring visits.

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

## 9.6 Warnings and Precautions

**Note:** Subjects must not receive any vaccinations from within 2 weeks of screening until 28 days after the final dose of study drug.

### 9.6.1 Infusion-Related Reaction

SYNT001 will be administered as an IV infusion over 1 hour ±15 minutes. Investigators may adjust the duration of the infusion if needed to increase tolerability. As with all mAbs administered by IV infusion, IRR are possible. In nonclinical testing of SYNT001 in NHPs, clinical observations were limited to IRRs due to the immunogenicity of SYNT001 in NHPs. These reactions included transient emesis/vomitus which typically occurred within one hour of dosing at all dose groups, but only after the third weekly infusion following the development of ADAs. Transient histamine-type responses were noted 30 minutes post-dose in some animals in all dose groups, but only following the third weekly infusion as above. These reactions were consistent with a histamine reaction (decreased activity, periocular swelling, erythema, facial flushing, eyelids partially/completely closed, and/or generalized weakness). With the exception of vomitus/emesis and red skin discoloration associated with injection or blood draw sites, these observations spontaneously resolved within 1-hour post-dose. Subsequent pretreatment with intramuscular diphenhydramine prevented further histamine-type reactions. All doses of SYNT001 were administered by bolus infusion over approximately 5 minutes in the NHP studies. Since xenobiotic hypersensitivity reactions commonly occur in NHPs following administration of humanized proteins, neither infusion reactions nor ADAs are considered predictive of immunogenicity or toxicity in humans (Bugelski and Treacy, 2004; ICH S6(R1), 2011; Ponce et al., 2009).

In general, infusion reactions to monoclonal antibodies observed in human studies typically develop within 30 minutes to 2 hours after the initiation of drug infusion, although symptoms

may be delayed for up to 24 hours. Most are mild in severity, although severe and even fatal reactions can occur.

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

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

Management of Grade 1 infusion reactions include interrupting the infusion or decreasing the rate of infusion by 50% and observing. Symptoms may also be treated as needed with medications such as diphenhydramine, hydrocortisone or acetaminophen, either alone or in combination, depending on the subject's signs and symptoms. If the infusion is interrupted or the infusion rate is decreased, it is important to note that all study drug infusions must be completed within 4 hours of SYNT001 administration. Management of Grade 2 and higher infusion reactions should include stopping the infusion of study drug. See Figure 2 and Figure 3 for details on the management of Grade 2 and Grade 3 infusion reactions. The severity of and management of allergic or infusion-related reactions will be graded and managed using NCI CTCAE Version 4.03 (see Table 8).

**Figure 2. Management of Moderate (Grade 2) Infusion Reactions**

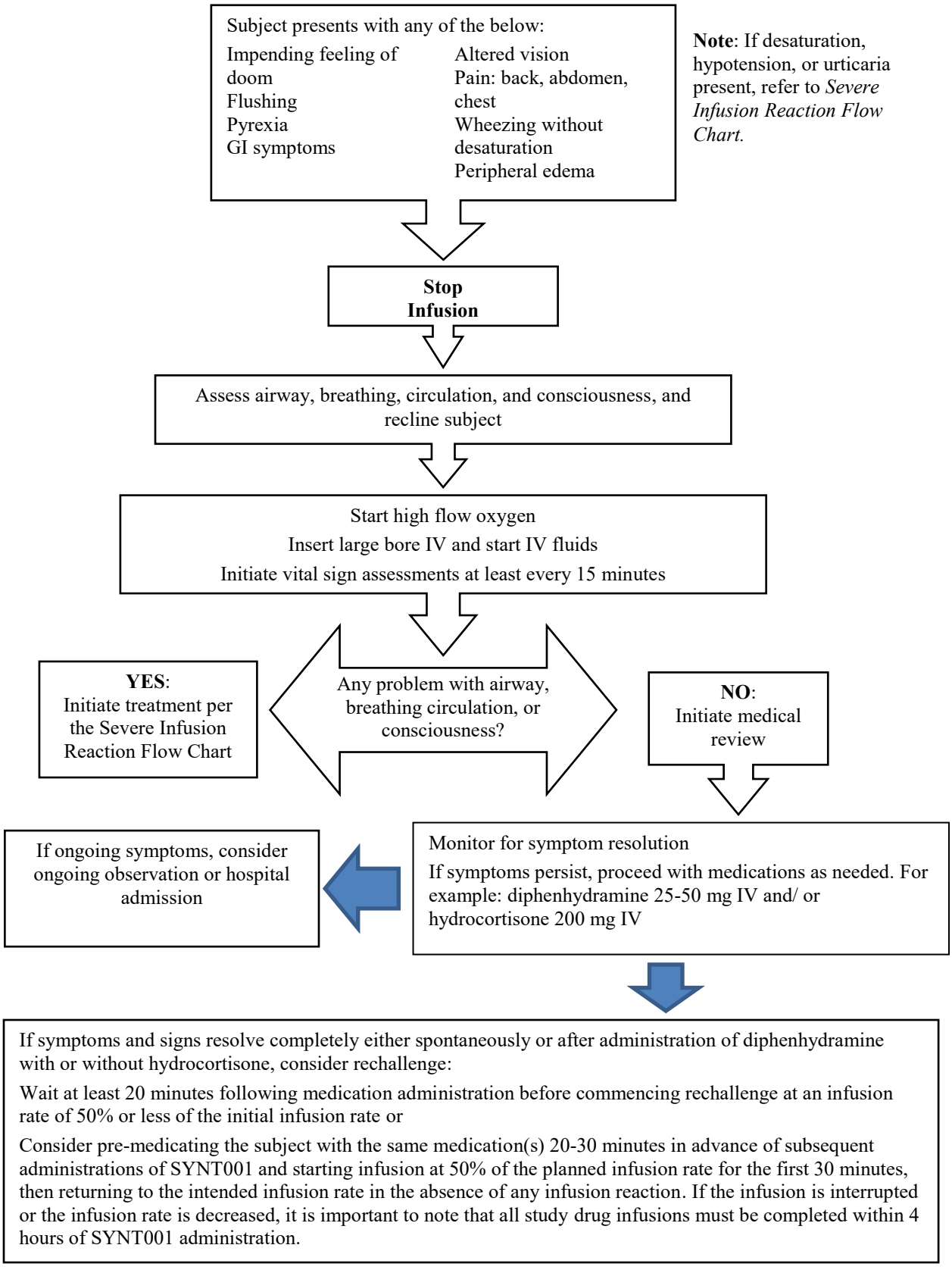

**Figure 3. Management of Severe (Grade 3 or Higher) Infusion Reactions**

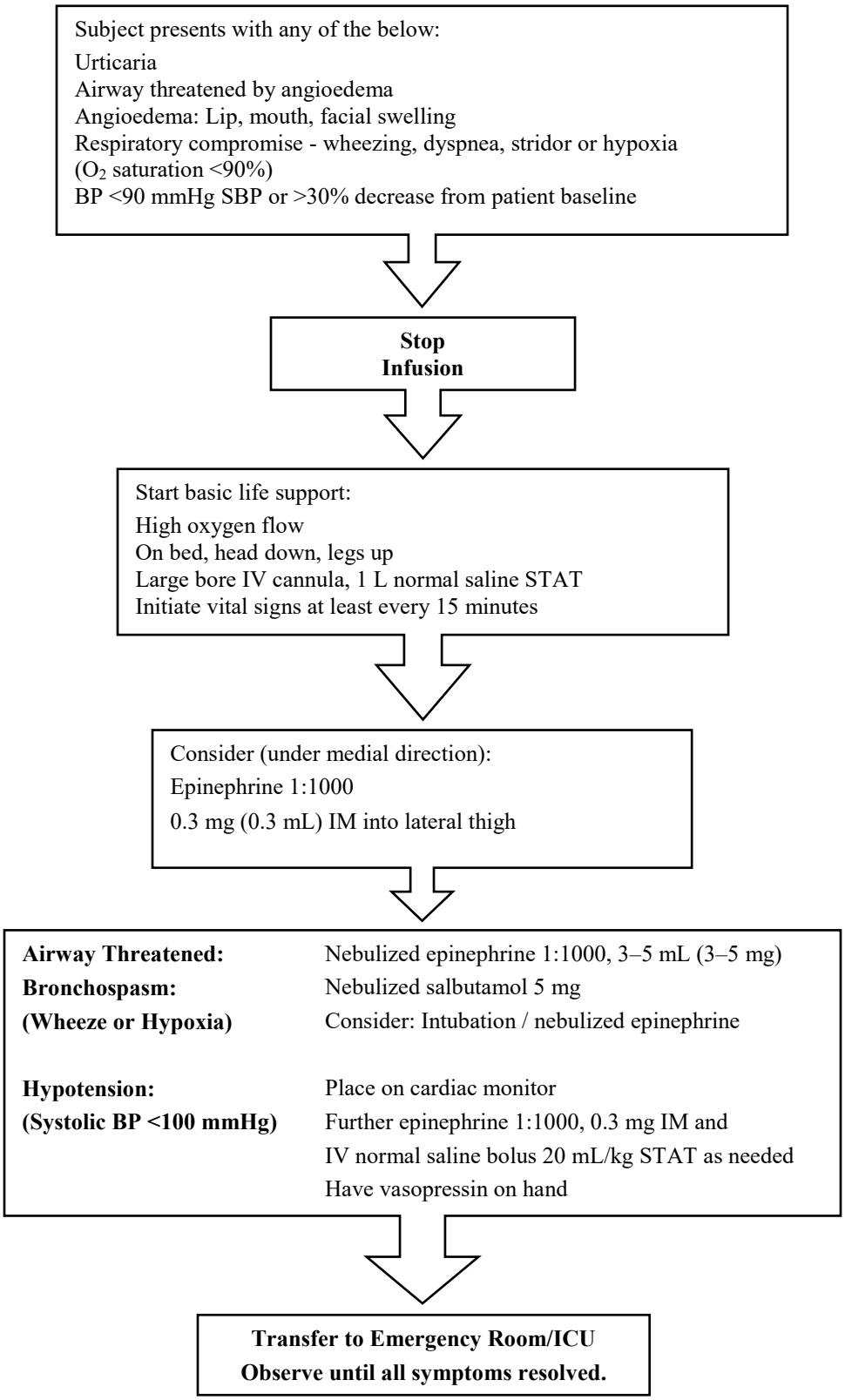

**Table 8. Grading and Management of Allergic or Infusion-Related Reactions**

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

Abstracted from NCI CTCAE Version 4.03.

### 9.6.3 Potential Immune Effects

An antibody blocking FcRn is anticipated to have several effects. These include acceleration of catabolism of IgG, but not other immunoglobulin isotypes such as IgA and IgM, leading to dose-dependent decreases in circulating IgG levels by up to an estimated 50% from the baseline levels

after a single dose and further decreases after multiple doses up to a 70% to 80% reduction. Based on studies in humans, it is expected that with a single dose, the nadir of this effect will occur approximately 5 days after dosing. The time course of recovery of IgG following dosing in the Phase 1a study suggests that a return to within 30% of baseline levels observed at pretreatment occurs within 4 weeks after a single dose and within 4 weeks after multiple doses as shown in NHPs.

Given the normal adult range of total IgG of 500 to 1600 mg/dL (Agarwal and Cunningham-Rundles, 2007; Furst, 2009; Gonzalez-Quintela et al., 2008; Jolliff et al., 1982; Keystone et al., 2007; McMillan et al., 1997; van Vollenhoven et al., 2013), with a mean of 1150 mg/dL, a 50% decrease in mean total IgG would translate to 575 mg/dL and a 50% decrease from the low end of the normal range used for the inclusion criteria of 600 mg/dL in this study would be to 300 mg/dL. An 80% decrease from baseline after multiple doses would result in IgG levels of 230 mg/dL and 120 mg/dL, respectively. While these levels are in the range found in patients with primary humoral immunodeficiency (Ameratunga et al., 2013), the levels will be transient. Further, in other conditions, the temporary (ie, less than 4 months) depletion of IgG (up to 95% reduction of total IgG as seen with immunoadsorption) does not appear to impart an increased risk of infection (Eming and Hertl, 2006; Furst, 2009; Keystone et al., 2007; Schmaldienst et al., 2001; van Vollenhoven et al., 2013). Study subjects will be monitored clinically for any infection. Further, commercial IVIG can be given to immediately restore IgG levels in case of a bacterial infection occurring while their IgG levels are decreased.

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

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

# 10. SAFETY

## 10.1 Safety Parameters

Clinical and laboratory AEs will be graded using the NCI CTCAE; Version 4.03 (see Appendix 1).

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

## 10.2 Adverse Event Definition

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

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

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

While pregnancy alone is not considered as an AE or SAE, any pregnancy complication(s) should be recorded as an AE(s) or SAE(s) (if applicable). Elective abortions without complications should not be regarded as AEs, unless they were therapeutic abortions (see below). Hospitalization for normal delivery of a healthy newborn should not be considered an SAE. If a female subject becomes pregnant during the conduct of the study, the Investigator must notify the Sponsor according to the procedures provided in Section 10.3.8).

## 10.3 Evaluating Adverse Events

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

### 10.3.1 Serious Adverse Events

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

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

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

- **Death:** This includes any death that occurs while the subject is “on study” through the last study visit.
  **Note:** Death is an outcome of an AE, and not an AE. The event(s) that caused death (eg, illness, accident) is the SAE. Death due to any other cause(s) must also be reported as an outcome of the reportable SAE.

- **Life-threatening adverse drug event:** An AE or suspected adverse reaction is considered “life threatening” if, in the view of either the Investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- **Inpatient hospitalization or prolongation of existing hospitalization:**
  In the absence of an AE, the Investigator should not report hospitalization or prolongation of hospitalization. This is the case in the following situations:

  - Hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol
  - Hospitalization or prolongation of hospitalization is part of routine procedure followed by study center
  - Hospitalization for survey visits or annual physicals
  - Hospitalization for observation with release within 24 hours

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

- **Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions**
- **Congenital anomaly/birth defect**
- **Important medical event:** An event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

### 10.3.2 Overdose

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

### 10.3.3 Non-Serious Adverse Events

*(Document on eCRF)*

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

### 10.3.4 Protocol-Related Adverse Events

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

### 10.3.5 Assessment of Causality

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

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

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

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

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

**Related:** Factors consistent with an assessment of Related include:

- There is a positive temporal relationship (eg, the event occurred within a reasonable time frame following administration of study medication); or
- The AE is more likely explained by the investigational product than by another cause (ie, the AE shows a pattern consistent with previous knowledge of the investigational product or the class of the investigational product)

### 10.3.6 Recording Adverse Events

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

### 10.3.7 Planned Hospitalization

A hospitalization planned by the subject prior to the first dose of study medication is considered a therapeutic intervention and not the result of a new SAE and should be recorded as medical history. If the planned hospitalization or procedure is executed as planned, the record in the subject's medical history is considered complete. However, if the event/condition worsens during the trial, it must be reported as an AE.

### 10.3.8 Reporting Pregnancies

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

If some of the information required for completion of the Pregnancy Reporting Form is unavailable at the time of the initial report, follow-up reports will be completed and submitted within 24 hours of becoming aware of the new information. Any pregnancy will be followed through delivery for the observation of any SAEs. Any SAE that occurs during pregnancy must be recorded on the SAE report form in the electronic data capture (EDC) system (eg, maternal serious complications, therapeutic or spontaneous abortion, ectopic pregnancy, stillbirth, neonatal death, congenital abnormality, birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs (See Section 10.3.9).

### 10.3.9 Serious Adverse Event Reporting

#### 10.3.9.1 Governing Regulatory Requirements

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

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

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

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

#### 10.3.9.2 Time Frame for Reporting

Any death, SAE, or pregnancy, experienced by the subject after informed consent through the last study visit, regardless of relationship to study drug, must be promptly reported (within 24 hours of the Investigator becoming aware of the event) by telephone or electronic transmission to the sponsor (or designee).

Contact information for **SAE** reporting:

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

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

**Medical Safety Contact**

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

#### 10.3.9.3 Information to be Provided by the Investigator

SAEs must be recorded on the SAE form in the EDC system. This requirement includes all SAEs that occur after informed consent through the last study visit.

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

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

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

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

### 10.3.10 Regulatory Reporting

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

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

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

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

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

## 10.4 Other Safety Considerations

### 10.4.1 Laboratory Data

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

### 10.4.2 Medication Errors

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

### 10.4.3 Follow-Up of Adverse Events

Any SAE or AE assessed as related to study drug must be followed until either resolution of the event or determination by the Investigator that the event has become stable or irreversible. The Investigator will follow all drug related AEs until there is a return to the subject's baseline condition, or until a clinically satisfactory resolution has been achieved. The appropriate follow-up visits must be scheduled and the specific tests repeated or performed as necessary. The status of all AEs will be documented as of the last study visit.

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

## 10.5 Safety Monitoring for Dose Escalation

Up to 8 subjects may be enrolled in Cohort 1. After 4 subjects reach Day 42, the Sponsor Medical Team will review available safety and PD data and will decide the dosing regimen for Cohort 2.

# 11. STATISTICAL CONSIDERATIONS

Statistical analyses will be performed using Statistical Analysis System (SAS) software (Cary, NC). All clinical data captured will be provided in data listings. A Statistical Analysis Plan (SAP) will be finalized prior to database lock.

## 11.1 General Design

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

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

## 11.2 Sample Size Justification

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

## 11.3 Statistical Considerations

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

Results will be summarized by cohorts.

### 11.3.1 Study Populations

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

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

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

### 11.3.2 Subject Accountability, Demographics, and Baseline Characteristics

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

#### 11.3.2.1 Baseline Analysis

Baseline characteristics to include medical history, physical examination, vital signs, and ECG will be summarized using descriptive statistics by dose and dose regimen.

### 11.3.3 Concomitant Medications

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

## 11.4 Planned PK Analysis

PK results will be summarized by dose regimen. Descriptive statistics of PK parameters for SYNT001 will include mean, SD, coefficient of variation (CV), median, minimum, and maximum.

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

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

## 11.5 Safety Analysis

The evaluation of SYNT001 based on vital signs, physical examination, ECGs, clinical safety laboratory tests, the incidence of AEs, TEAEs, and SAEs will be summarized by dose and dose regimen, severity, and relationship to study drug.

Treatment-emergent AEs will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA®; Version 19 or higher) System Organ Class (SOC) and preferred term, classified from verbatim terms. The incidence and percentage of subjects with at least 1 occurrence of a preferred term will be included, using the most severe grade. The number of events per preferred term will also be summarized. Causality (relationship to study drug [related/not related]) will be summarized separately.

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

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

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

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

## 11.6 Pharmacodynamic Analysis

Disease activity marker results (hematocrit, hemoglobin, platelet count, reticulocyte count, LDH, haptoglobin, total and indirect bilirubin, and direct Coombs test) will be summarized by dose and dose regimen. Descriptive statistics of PD will include mean, SD, median, minimum, and maximum.

## 11.7 Immunogenicity Analysis

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

## 11.8 Interim Analysis

No formal interim analysis is planned. Safety and PD results will be examined on an ongoing basis for making dose-escalation decisions; no statistical analyses are planned for aiding these dose-escalation decisions.

# 12. DATA QUALITY ASSURANCE

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

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

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

# 13. STUDY ADMINISTRATION

## 13.1 Study Administrative Structure

The study administration structure is provided in Table 9.

**Table 9. Study Administrative Structure**

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

## 13.2 Ethical Conduct of the Study

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

## 13.3 Informed Consent (ICF)

A properly executed, written informed consent document, in compliance with 21 CFR, Part 50 and the ICH guidelines, will be obtained from each subject before the subject is entered into the study and before any study screening procedure is performed that involves risk. Attention will be directed to the basic elements required for incorporation into the informed consent under US Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a]) and (21 CFR 50.25[b]), as necessary.

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

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

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

## 13.4 Institutional Review Board

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

## 13.5 Dose Escalation Committee

The DEC will perform the 24-hour safety data review for the first subject in Cohort 1 to ensure that there are no overt safety concerns before dosing the second subject. The DEC will also review the 7-day safety data for the first 2 subjects in Cohort 1 prior to dosing the remaining subjects in the cohort.

## 13.6 Sponsor Medical Team

The Sponsor Medical Team will consist of at least the Medical Monitor and the Sponsor Medical Lead.

After 4 subjects in Cohort 1 reach Day 42, the Sponsor Medical team will review available safety and PD data and will decide the dosing regimen for Cohort 2. The Sponsor Medical Team will also perform the 24-hour safety data review for the first subject in Cohort 2 to ensure that there are no overt safety concerns before dosing the second subject in Cohort 2, The Sponsor Medical Team will review the 7-day safety data for the first 2 subjects in Cohort 2 prior to dosing the remaining subjects in the cohort. In addition, the Sponsor Medical Team will, on an ongoing basis, review Safety and PD data.

## 13.7 Future Use of Subject Samples

Not all the tissue and blood components obtained during this study may be required for the tests that are part of the clinical trial. Available samples may be used for additional analyses and research. This research will help to understand disease subtypes, drug response and AE, and possibly identify new drug targets or biomarkers that predict subject response to treatment. The use of the samples for internal research will be done using the guidelines defined by the FDA guidance for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individual Identifiable (issued 25 April 2006) and the European Medicines Agency Reflection Paper on Pharmacogenetic Samples, Testing and Data Handling (Doc. Ref. EMEA/CHMP/PGxWP/201914/2006; 15 November 2007). If a subject requests destruction of their tissue and blood samples and the samples have not yet been de-identified, the Sponsor will destroy the samples as described in this FDA guidance. The Sponsor will notify the Investigator in writing that the samples have been destroyed.

# 14. CONDITIONS FOR MODIFYING THE PROTOCOL

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

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

# 15. CONDITIONS FOR TERMINATING THE STUDY

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

# 16. STUDY DOCUMENTATION, CRFS, AND RECORD KEEPING

## 16.1 Investigator's Files and Retention of Documents

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

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

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

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

## 16.2 Source Documents and Background Data

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

These records include detailed notes on the following:

- Medical history
- Date and time of informed consent with Health Insurance Portability and Accountability Act (HIPAA) authorization either contained in the ICF or presented to the subject candidate as a standalone document
- Description of the complete consenting process
- The basic identifying information that linked the subject's medical record with the eCRFs
- The results of all diagnostic tests performed, diagnoses made, therapy provided, and any other data on the condition of the subject

- The medical condition of the subject during their involvement in the study
- All AEs
- The subject's exposure to the study medication
- The subject's exposure to any concomitant therapy
- All relevant observations and data on the condition of the subject throughout the trial
- Justification for all entries in the subject's eCRF

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

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

## 16.3 Audits and Inspections

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

## 16.4 Electronic Case Report Forms

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

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

# 17. MONITORING THE STUDY

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

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

# 18. CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

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

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

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

# 19. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

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

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

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# APPENDIX 1. NCI CTCAE, VERSION 4.03

# APPENDIX 2. KARNOFSKY PERFORMANCE SCALE

| General Category | Index | Specific Criteria |
|---|---|---|
| Able to carry on normal activity; no special care needed. | 100% | Normal, no complaints, no evidence of disease. |
| | 90% | Able to carry on normal activity, minor signs or symptoms of disease. |
| | 80% | Normal activity with effort, some signs or symptoms of disease. |
| Unable to work, able to live at home and care for most personal needs, varying amount of assistance needed. | 70% | Cares for self, unable to carry on normal activity or to do work. |
| | 60% | Requires occasional assistance from others but able to care for most needs. |
| | 50% | Requires considerable assistance from others and frequent medical care. |
| Unable to care for self, requires institutional or hospital care or equivalent, disease may be rapidly progressing. | 40% | Disabled, requires special care and assistance. |
| | 30% | Severely disabled, hospitalization indicated, death not imminent. |
| | 20% | Very sick, hospitalization necessary, active supportive treatment necessary. |
| | 10% | Moribund. |
| | 0% | Dead. |

Source: Mor V, Laliberte L, Morris JN, Wiemann M. The Karnofsky Performance Status Scale. An examination of its reliability and validity in a research setting. Cancer. 1984;53(9):2002-2007.

# APPENDIX 3. COHORT 2 ALTERNATIVE WEEKLY MAINTENANCE SCHEDULE OF EVENTS TABLE

## Table 10. 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 | | |

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| 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 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 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 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 Section 6.7.4 for additional information.

i. **Immunogenicity:** Samples will be collected pre-dose when collected on dosing days. See Section 6.7.6 for additional information.

j. Prior to **study drug infusion**, SYNT001 drug product is to be diluted in dextrose 5% in water to a total volume of 250 mL and administered intravenously over 1 hour ±15 minutes using a 0.2-micron, inline filter. See Section 9 for additional information.

k. **Immunoglobulins (IgG, IgA, IgM) and IgG subtypes (IgG 1-4):** Collected for measurements of IgG, IgG subtypes (IgG1-4), IgA, and IgM at every visit. On dosing days, samples are collected prior to infusion of study drug. See 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 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.