

STATISTICAL ANALYSIS PLAN

Study Title: A Randomized, Double-Blinded, Placebo-Controlled Study of the Effect of XmAb®5871 on Systemic Lupus Erythematosus Disease Activity

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STATISTICAL ANALYSIS PLAN APPROVAL

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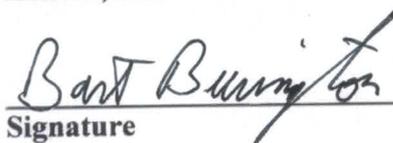
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TABLE OF CONTENTS

Section	Page
1. INTRODUCTION	7
2. OVERVIEW OF STUDY DESIGN	7
2.1 Primary Objective.....	10
2.2 Secondary Objectives	10
2.3 Exploratory Objectives.....	10
3. SAMPLE SIZE JUSTIFICATION	11
4. RANDOMIZATION, BLINDING AND DROP OUTS	11
5. DEFINITIONS OF PATIENT POPULATIONS TO BE ANALYZED.....	12
5.1 Enrolled Population	12
5.2 Intent-to-Treat (ITT) Population	12
5.3 Safety Population.....	12
5.4 Efficacy Evaluable Population	12
5.5 Pharmacokinetic/Immunogenicity Population	13
5.6 Pharmacodynamic Population:.....	13
6. DEFINITIONS, COMPUTATIONS, DATA CONVENTIONS.....	13
6.1 Definitions and Computations.....	13
6.2 Conventions.....	14
7. MISSING DATA AND DROPOUTS	15
7.1 Partial/Missing Dates for Study-Related Visits or Procedures:	15
7.2 Partial/Missing Dates for Adverse Events.....	15
8. DESCRIPTION OF STATISTICAL ANALYSES	16
8.1 General Principles	16
8.2 Patient Enrollment, Disposition, Protocol Deviations.....	16
8.3 Demographics and Baseline Characteristics	17
8.4 Additional Baseline Characteristics	17
8.5 Physical Examination and Medical History/Concurrent Illness.....	17
8.6 Prior and Concomitant Therapy	17
8.7 Study Treatment Administration, Exposure and Procedure	17
8.8 Efficacy and Exploratory Analysis.....	18
8.8.1 Primary Efficacy Endpoint (Loss of Improvement at Day 225)	18
8.8.2 Secondary Efficacy Endpoints	19
8.8.3 Exploratory Efficacy Endpoints.....	21
8.9 Safety Analysis.....	21
8.9.1 Treatment Emergent Adverse Events.....	21

8.9.2	Serious Adverse Events.....	22
8.9.3	Adverse Events Leading to Discontinuation from Study.....	22
8.9.4	Deaths.....	22
8.9.5	Clinical Laboratory Tests.....	22
8.9.6	Vital Signs.....	24
8.9.7	12-Lead Electrocardiogram.....	25
8.10	Pharmacokinetics (PK).....	25
8.11	Pharmacodynamics (PD).....	26
8.12	Pharmacokinetic/Pharmacodynamic Analyses.....	26
8.13	Immunogenicity: Human Anti-Human Antibodies (AHA).....	26
8.14	Pharmacogenomics.....	26
9.	INTERIM ANALYSIS.....	27
10.	TESTING/VALIDATION PLAN AND SOFTWARE SYSTEM.....	27
11.	STATISTICAL ANALYSIS CHANGES FROM THE PROTOCOL.....	27
12.	REFERENCES.....	28
13.	SCHEDULE OF ASSESSMENTS.....	29
APPENDIX 1.	IMPUTATION OF PARTIAL AND MISSING DATES.....	31

ABBREVIATIONS AND DEFINITIONS

Ab	Antibody
ABC	Absolute B cell count
AE	Adverse event
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
ATC	Anatomical therapeutic chemical
BILAG	British Isles Lupus Activity Group (version BILAG2004)
BMI	Body Mass Index
bpm	Beats per minute
BP	Blood pressure
BUN	Blood urea nitrogen
CI	Confidence interval
CPK	Creatine phosphokinase
CS	Clinically significant
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOI	End of infusion
EOS	End-of-study
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
Fv	Antibody variable
GCP	Good Clinical Practices
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
HAHA	Human anti-human antibodies
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
ICH	International Committee for Harmonization
Ig	Immunoglobulin
IP	Investigational Product
IQR	Interquartile Range
ITT	Intent to Treat
IU	International units

IV	Intravenous
K-M	Kaplan-Meier
LDH	Lactate dehydrogenase
mAb	Monoclonal antibody
mmHg	Millimeters of mercury
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NCS	Not clinically significant
PD	Pharmacodynamic
PGA	Physician's Global Assessment
PK	Pharmacokinetic
PT	Prothrombin time
PPD	Pharmaceutical Product Development (clinical research organization)
PPT	Partial Prothrombin time
RI	Responder Index
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SBP	Systolic blood pressure
SD	Standard deviation
SDS	System Documentation Specifications
SE	Standard error of the mean
SELENA SLEDAI	SLE disease activity index as modified in the SELENA study
SLE	Systemic Lupus Erythematosus
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
UNK	Unknown
VAS	Visual Activity Scale
WHO-DD	World Health Organization - Drug Dictionary

1. INTRODUCTION

The Statistical Analysis Plan (SAP) describes the data analysis specifications for Xencor, Inc. protocol XmAb5871-04 titled: “*A Randomized, Double-Blinded, Placebo-Controlled Study of the Effect of XmAb®5871 on Systemic Lupus Erythematosus Disease Activity*”. It details the inferential statistical methodology to be used in analyzing study data and outlines the statistical programming specifications, tables, figures, and listings. It describes the variables and populations, anticipated data transformations and manipulations, and other details of the analyses not provided in the clinical study protocol. Additional purposes of the SAP are to serve as a communication tool between Vantage Data Designs, Inc. and Xencor, Inc. with respect to expected statistical data outputs after database lock and to allow SAS Programming of the tables, listings, figures to commence as early in the process as possible.

This version of the statistical analysis plan was prepared in accordance with the protocol XmAb5871-04 Version 2.0 dated July 29, 2016. Other related documents are the electronic case report forms (eCRFs), eCRF completion guidelines (with screenshots) from PPD, and System Documentation Specifications (SDS) document from Medidata RAVE.

This SAP supersedes the statistical considerations identified in the protocol. The SAP will be finalized prior to database lock and describes the statistical analysis as it is foreseen when the study is being planned. If circumstances should arise during the study rendering this analysis inappropriate, or if in the meantime improved methods of analysis should come to light, different analyses may be made. Any deviations from the SAP after database lock, reasons for such deviations and all alternatives or additional statistical analyses that may be performed, will be described in a SAP Addendum.

2. OVERVIEW OF STUDY DESIGN

Experimental Design: Phase 2, randomized, double-blind, placebo-controlled, multi-center study in patients with Systemic Lupus Erythematosus (SLE) Disease.

Allocation of treatment: Two randomized treatment arms. Participants will receive either 5 mg/kg XmAb5871 or placebo (1:1 treatment allocation) by IV infusion every other week for up to a total of 16 infusions.

Number of patients planned: A total of approximately 90 patients will be enrolled in up to 25 sites. Patients who are lost to follow up or withdraw consent for study participation prior to randomization and study drug administration may be replaced, at sponsor’s discretion.

Treatment and Study Duration: After up to a 4-week screening period, participants will receive XmAb5871 or placebo by IV infusion every other week for up to a total of 16 doses (30 weeks) and will be followed for 6 weeks following the last dose for a total study period of up to 40 weeks.

Study Procedures: Eligible patients must have moderate to severe, non-organ threatening, SLE activity defined as a SELENA SLEDAI of ≥ 6 (≥ 4 points of which must come from non-serological findings) OR ≥ 1 BILAG B score OR ≥ 1 BILAG A score. Patients must be able and willing to discontinue background immunosuppressive medications and to receive a brief course of IM steroid therapy to enter screening.

After obtaining informed consent, 160 mg of IM depomedrol will be administered and screening studies will be performed. Over the 2-4 week period following the initial IM depomedrol, per investigator discretion, patients may receive additional IM depomedrol (up to an additional 320 mg during screening) to treat their SLE symptoms to a target of disease activity improvement defined as a SELENA SLEDAI decrease of ≥ 4 points OR a decrease in BILAG of ≥ 1 severity grade in at least one organ system that began with A or B (clinical criteria without requiring temporal criteria). Immunosuppressive therapy will be stopped or tapered off over the 2-4 week screening period and must be discontinued by randomization on Day 1. Patients on anti-malarial therapy may continue on their usual dose. Patients entering the study on oral doses of ≤ 15 mg of prednisone per day (or the equivalent) will taper their oral steroids to 10 mg per day or less by randomization (Day 1) and then may continue on a ≤ 10 mg daily dose through the study. Patients who do not meet the disease activity improvement criteria during the 2-4 week screening period will not be randomized into the study and their participation will end.

Patients must have documented disease activity improvement following the brief course of IM steroid therapy during the screening period to be randomized into the study on Day 1. Those patients who achieve the required disease activity improvement from the screening baseline will be randomized to receive either XmAb5871 (5 mg/kg) or matching placebo by IV administration (double-blinded) over 1-2 hours every 2 weeks from Day 1 through Day 211 for a total of up to 16 infusions. Disease activity (SELENA SLEDAI, BILAG) on Day 1 will be considered the baseline disease activity for determination of the efficacy endpoints. On Day 1, 80 mg of IM depomedrol will be administered and baseline procedures including physical exam, blood and urine samples for laboratory assessments, PK and PD samples will be performed. The first infusion of XmAb5871 or placebo will be given IV over a period of 2

hours. Patients will be observed for at least 2 hours after completion of the first study drug administration during which time safety assessments will be performed.

All patients will return to the research facility on Day 8 for safety, PK and PD assessments. On study Day 15, patients will receive 80 mg of IM depomedrol in addition to the procedures scheduled for that day and will receive the second IV infusion of XmAb5871 or placebo. Patients will return on study Days 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, 169, 183, 197, and Day 211 for XmAb5871 or placebo administration IV over 1-2 hours and for safety, PK and PD assessments. Patients will be required to remain at the study site for observation for at least 1 hour after the completion of each infusion.

Patients will be followed for the loss of disease activity improvement (LOI) as defined by:

- I. The assessment by the investigator that SLE disease activity is appropriate for an increase in therapy (including addition of another lupus therapy, except for adjustments in NSAIDs) AND
- II. There has been one of the following compared to baseline (Day 1):
 - 1) a SELENA SLEDAI increase of ≥ 4 points from maximal improvement OR
 - 2) a worsening of at least 1 BILAG A or B score OR
 - 3) the appearance of a new BILAG A or B score.

Patients who meet the criteria for loss of disease activity improvement at any timepoint up to and including Day 211 will not receive further infusions of XmAb5871 or placebo and may receive any appropriate SLE therapy at the discretion of the principal investigator.

The effect of XmAb5871 on loss of improvement of SLE disease activity will be evaluated as the percentage of patients without loss of disease activity improvement at Day 225 (primary endpoint) and Day 169 (secondary endpoint). Patients with loss of disease activity improvement at any time-point up to and including Day 225 will be considered non-responders for the primary endpoint. Patients who discontinue the study early either because of loss of improvement or for other reasons will be followed for a further period of 6 weeks after their last dose of XmAb5871 or placebo.

All patients completing the treatment period should be followed through Day 253 (EOS). Patient participation is complete once EOS study procedures are performed. All AE(s) (including serious AEs and deaths) and use of concomitant medication information will be collected throughout the study from screening through the EOS visit. Patients developing

treatment-emergent AEs (TEAEs) or clinically significant safety lab abnormalities will be followed until resolution or until the TEAEs/abnormalities are stabilized.

Schedule of Assessments: The study consists of a Screening visit (Day -28 to Day -1) followed by sixteen infusions of XmAb5871 given every two weeks (Days 1, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141 155, 169, 183, 197, and Day 211) with collection of disease activity assessments, safety data, PK, and PD. Patients will be seen on Day 8 for safety monitoring, PK and PD and will be followed for 6 weeks after the final infusion (Days 225 and 253 [EOS]). Patients who experience loss of disease activity improvement will have their study drug infusions discontinued and will receive appropriate SLE rescue therapy at the discretion of the principal investigator. The patient should be followed for an additional 6 weeks from the time of the last study drug infusion. Assessments listed for the Day 225 visit should be performed at the time of loss of disease activity improvement (LOI). Assessments listed for the Day 253 (EOS) visit should be performed at the follow-up visit 6 weeks from the time of the last study drug infusion. The maximal study duration for an individual patient will be 253 days after the first infusion.

Please see Section 13 of this SAP for the Schedule of Assessments.

Data collection: Electronic Case Report Form (eCRF) using Medidata RAVE platform and administered by PPD.

2.1 Primary Objective

To determine the ability of XmAb5871 to maintain SLE disease activity improvement achieved by a brief course of disease-suppressing intramuscular (IM) steroid therapy in SLE patients.

2.2 Secondary Objectives

- To evaluate time to loss of SLE disease activity improvement achieved by a brief course of disease-suppressing IM steroid therapy in SLE patients
- To evaluate the safety and tolerability of every other week intravenous (IV) administration of XmAb5871 in patients with SLE
- To evaluate the pharmacokinetics (PK) and immunogenicity of every other week IV administration of XmAb5871 in patients with SLE

2.3 Exploratory Objectives

To characterize the pharmacodynamics (PD) of every other week IV administration of XmAb5871 in patients with SLE as follows:

- To evaluate the effect of XmAb5871 on changes in the absolute B Cell count (ABC)
- To characterize the effect of XmAb5871 on SLE disease activity over time
- To evaluate the effect of XmAb5871 on autoantibody, complement and cytokine levels

3. SAMPLE SIZE JUSTIFICATION

It is anticipated that approximately 90 patients will be enrolled in the study. Sample size is based on a previously completed study of SLE patients treated with IM depomedrol for 2 weeks following cessation of background immunosuppressant therapy. In that study, by month 6, 40/41 patients lost the disease activity improvement achieved following IM steroid therapy; a 2.4% placebo response.

Assuming a 10% placebo response (defined as no loss of disease activity improvement from Day 1 to Day 169) and a 38% response in the XmAb5871 treatment arm (i.e., a 28% delta between treatment arms), 40 patients per treatment arm will provide 80% power to detect this difference at $\alpha=0.05$ (two-sided) by use of the Fishers exact test. Adding 10% for unevaluable patients, the total number per arm is calculated as 45.

4. RANDOMIZATION, BLINDING AND DROP OUTS

Approximately 90 patients will be randomized in a 1:1 treatment allocation scheme; therefore, 45 patients will be assigned to the XmAb5871 arm and 45 patients assigned to the placebo arm. There are no stratification factors planned for this randomization. A clinical research organization independent of the clinical trial team will develop the randomization schedule and the actual randomization assignment will be made through a secure Interactive Web-Based System (IWRS).

After obtaining oral and written informed consent, patients will be screened according to the inclusion and exclusion criteria. The screening number will be used throughout the screening period. Patients who meet all selection criteria will then be randomized and receive a patient number on Day 1. The patient number will ensure identification throughout the study.

The study will be conducted in a double-blind manner. All patients, investigators, and study staff/clinicians will be blinded to the study treatment assignment (XmAb5871 or Placebo) until the study is formally unblinded for data analysis purposes. The Sponsor's team members responsible for study conduct and safety monitoring will also be blinded to study treatment. The randomization schedule will be held at an independent clinical research

organization not affiliated with the study conduct and will only release the full randomization schedule after the database is formally locked for data analysis purposes.

However, individual patient treatment assignment may be revealed due to the occurrence of a medical emergency requiring medical intervention or if the Medical Monitor for the study determines that patient safety requires knowledge of the study drug assignment.

Documentation of the breaking of the randomization code, including the date and reason for such unblinding, must be documented in the EDC system.

Patients dropping-out or withdrawing, for any reason, without completing all screening evaluations successfully, will be considered as “screening failures “. Such patients will not receive a patient number; however, screening data will be collected in the electronic Case Report Forms (eCRFs). The Investigator will keep a screening log of all patients screened to assess the numbers and characteristics of the excluded patients, and the reasons for their exclusion.

5. DEFINITIONS OF PATIENT POPULATIONS TO BE ANALYZED

5.1 Enrolled Population

Defined as all patients who were enrolled in the study (signed informed consent, met inclusion and exclusion criteria and were randomized), whether or not the study drug was administered.

5.2 Intent-to-Treat (ITT) Population

Defined as all patients randomized and who have received at least a partial dose of XmAb5871 or placebo.

5.3 Safety Population

Defined as all patients who received at least a partial dose of XmAb5871 or placebo. In this study, this is equivalent to the ITT population.

5.4 Efficacy Evaluable Population

Defined as all patients who:

- Complete study through Day 225 assessments
- Discontinue due to reaching the protocol specified LOI endpoint (and have not missed 2 or more consecutive doses prior to the LOI visit)
- Discontinue due to drug-related adverse event (nonresponder)

5.5 Pharmacokinetic/Immunogenicity Population

The Pharmacokinetic population will include all patients with at least one pre-dose and one post-dose evaluable result reported. All patients who received XmAb5871 and have at least 1 post-IMP dosing ADA sample drawn will be included in the immunogenicity population.

5.6 Pharmacodynamic Population:

Defined as all patients who have received XmAb5871 and for whom the PD data are considered to be sufficient and interpretable will be analyzed in the PD analyses.

6. DEFINITIONS, COMPUTATIONS, DATA CONVENTIONS

6.1 Definitions and Computations

Screening

Screening is defined as Day -1 (Visit 1) prior to the first study drug administration.

Baseline

Baseline represents the procedures or assessments done prior to the first administration of XmAB5871 or placebo. Baseline could possibly be the screening visit under this definition.

Visit Dates

For ease of data analysis and summary table presentations, the nominal visit day nomenclature (see chart below) will be used. See Appendix 13 for more details.

Study Phase	Day
Screening	-1
Treatment	1, 8, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, 169, 183, 197, 211 (last study drug administration) and 225
End of Study	253

Adverse Event (AE)

AEs will be collected and recorded for each patient from the date the informed consent form (ICF) was signed (Screening) until the end of their participation in the study, i.e., the patient has discontinued or completed the study.

The definitions of AE terms are guided by the United States Code of Federal Regulations (21 CFR 312.32) and are included in Section 6.1.2.1 of the study protocol. Please use the study protocol if further information is needed.

Treatment Emergent Adverse Event (TEAE)

Adverse medical events occurring after the Date of Informed Consent but before the first dose of study drug will be recorded as non-treatment emergent AEs on the AE case report form. AEs are considered “treatment-emergent” if the start date for a new event or a grade increase for an existing AE starts on or after the date of the first dose.

Efficacy Endpoints

The type, definition, and calculation of each of the efficacy endpoint are described in detail within Section 8.8 of this SAP.

Safety Endpoints

The type, variables collected, timepoints collected, and calculation of each of the safety endpoint are described in detail within Section 8.9 of this SAP.

6.2 Conventions

- 1 year = 365.25 days. Year is calculated as (days / 365.25) and will be rounded to 1 digit after the decimal point (tenths) for presentation purposes.
- 1 month = 30.4375 days. Month is calculated as (days / 30.4375) and will be rounded to 1 digit after the decimal point (tenths) for presentation purposes.
- 1 pound = 0.454 kg and 1 kg = 2.2 pounds
- 1 inch = 2.54 cm and 1 cm = 0.3937 inches
- Body mass index (BMI) calculated as $[\text{weight (lbs)} / \text{height (in)}^2] \times 703$
- BMI using metric system: $[\text{weight (kg)} / [\text{height (m)}]^2]$
- Age will be calculated in years relative to the date of study consent based on the following SAS statement: $\text{Age} = ([\text{Consent Date} - \text{Date of Birth}] / 365.25)$ and will be rounded down to the nearest integer for presentation purposes.
- Investigational Product (Study Drug) is XmAb5871 and Comparator Product is Placebo.
- Unless otherwise specified, percentages will be calculated based on the number of patients specified by the appropriate population definition.
- The software used for all summary statistics and statistical analyses will be SAS Version 9.4 or later.

- All tables, listings, figures will be produced in landscape orientation using Times New Roman 9-point font. Output files will be created in rich text file (RTF) format.
- Missing or invalid data will be generally treated as missing, not imputed, unless otherwise stated (see Section 7).

7. MISSING DATA AND DROPOUTS

The issue of how to handle missing data caused by dropouts in clinical studies is a research topic that is still under development in the statistical literature. As has been noted in the ICH-E9 guideline, “no universally applicable method of handling missing values can be recommended”. The best approach is to minimize the chance of missing data / dropouts at the design stage of the clinical study and during study monitoring.

In general, data will be analyzed as received from the clinical database. Hence, missing values will not be imputed except for the following situations:

7.1 Partial/Missing Dates for Study-Related Visits or Procedures:

It is anticipated that all study-related visit and procedure dates entered into the clinical study database will be complete (i.e. day, month, year are all recorded) and accurate. Any missing or partially missing date of this type will be queried before statistical analyses are performed. If the day, month, and/or year are still unknown, then the dates will be imputed as follows for purposes of analysis:

- If the day of the visit or procedure date is missing, then take the previous visit and add the number of days to the next visit according to the visit schedule.
- If the month of the visit or procedure date is missing then take the previous visit and add the number of months to the next visit according to the visit schedule.
- If the year of the visit or procedure date is missing, then the year will be queried. If the year is unknown, no imputation of year will take place.

Imputed dates will be noted in the patient data listings.

7.2 Partial/Missing Dates for Adverse Events

Rules for imputing partial/Missing dates are detailed in Appendix 1.

8. DESCRIPTION OF STATISTICAL ANALYSES

8.1 General Principles

Unless otherwise noted, data will be summarized in tabular format by XmAb5871 or Placebo treatment group using summary tables and data listings. For this Phase 2 study, a patient who is enrolled but does not receive study drug will be excluded from the data summary tables. Data summaries will only include patients that receive study drug. All study data documented on the eCRFs will be included in the study data listings.

Given this is a randomized placebo-control study; inferential statistical methodologies are planned and any statistical tests are utilized they will be two-sided, with type 1 error rate of 5%. All confidence intervals (if constructed) will be constructed at the 95% confidence level. No p-value adjustments on the secondary efficacy endpoints for multiplicity analyses will be made.

Data will be summarized with respect to enrollment and disposition summaries, demographics and baseline characteristics, concomitant medications, efficacy, and safety measures. Summary (i.e. descriptive) statistics will include N, mean, standard deviation, median, range (minimum, maximum) values for continuous variables and frequencies, and percentages for categorical variables. Time-to-event analyses will be summarized using Kaplan-Meier survival analysis and figures for the estimated median time.

Missing or invalid data will be generally treated as missing, not imputed, unless otherwise stated (see Section 7).

8.2 Patient Enrollment, Disposition, Protocol Deviations

- Patient enrollment by site along with number of patients evaluable for safety, ITT, evaluable for efficacy populations will be tabulated.
- The number of patients completing the study and number withdrawing the study with the primary reason for withdrawal (Loss of Improvement, AE, physician recommendation, withdrew consent, lost to follow-up, or other reasons) will be tabulated.
- A protocol deviation is any noncompliance with the clinical trial protocol or Good Clinical Practice (GCP). The noncompliance may be either on the part of the patient, the investigator, or the study site staff. Since protocol deviations are not part of the eCRF database, they will be identified and documented by Xencor study

monitors/project manager based on a review of data listings prior to database lock. Protocol deviations will be listed.

8.3 Demographics and Baseline Characteristics

A summary of age, gender, race, ethnicity, height, weight, and BMI will be presented using appropriate descriptive statistics.

The categorical (discrete) variables will be summarized using counts and percentages. The continuous variables will be summarized using mean, median, standard deviation, and range (maximum, minimum). These summaries will include patients in the ITT population.

8.4 Additional Baseline Characteristics

The time (months) from date of diagnosis of Lupus disease to randomization date and depomedrol administration / dose amount will be summarized using descriptive statistics. SLE associated symptoms will be recorded in SLEDAI and BILAG worksheets and these baseline characteristics will be presented in the corresponding efficacy tables. Pharmacogenomics and FSH will also be summarized with baseline characteristics.

8.5 Physical Examination and Medical History/Concurrent Illness

All Physical Exam and Medical History/Concurrent Illnesses data will be presented in patient listings.

8.6 Prior and Concomitant Therapy

All medications taken before a patient's first dose will be reported as prior medications in patient listings. All medications taken since the time of first dose until the end of the study will be classified as concomitant medications. These medications will be coded using WHO Drug Dictionary (WHODD), version 201509. The number and proportion of patients in the Safety population using concomitant medications will be tabulated and summarized in a table by WHODrug anatomical class (ATC) and preferred drug name. These data will also be presented in patient listings.

8.7 Study Treatment Administration, Exposure and Procedure

There are sixteen infusions of XmAb5871 (or placebo) planned every two weeks (Days 1, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, 169, 183, 197, and 211).

Exposure to study treatment (XmAB5871 or placebo) will be demonstrated by calculating the days of exposure (date of first dose of study drug to the last dose date of study treatment) and the number of infusions. These will be tabulated using descriptive statistics.

Study treatment administration procedure will be described by “Was Study Drug Administered” (Yes/No), “Was Infusion Completed” (Yes/No), and “Was Study Drug Administration Interrupted” (Yes/No) for each visit study treatment was administered.

Patient listings will be prepared showing the patient number, whether or not drug was administered at that specific visit, reasons why not, lot number, date and time of dose administration, planned volume/dose, actual total volume/dose administered, dose interruptions, dose restart, and reason for dose interruption.

8.8 Efficacy and Exploratory Analysis

Efficacy analyses will be performed on the Efficacy Evaluable and ITT Populations. The Efficacy Evaluable will serve as the primary population for all efficacy analyses and the ITT will be conducted for sensitivity analysis purposes.

Efficacy parameters: SELENA SLEDAI, BILAG 2004, and Physician’s Global Assessment (PGA) will be collected at Screening, Days 1, 29, 57, 85, 113, 141, 169, 197, 225 and 253.

8.8.1 Primary Efficacy Endpoint (Loss of Improvement at Day 225)

The primary endpoint will be evaluated as the percentage of SLE patients without loss of disease activity improvement from Day 1 to Day 225 (i.e., responders). Loss of improvement will be defined as worsening of disease activity that in the opinion of the principal investigator requires a change in treatment (exclusive of a decrease in oral steroids) AND one of:

- 1) SELENA- SLEDAI increase of ≥ 4 points from maximal improvement OR
- 2) Worsening of at least 1 BILAG A or B score OR
- 3) New BILAG A or B score.

The LOI parameter will be taken directly from the eCRF (Form Name: Loss of Improvement, Variable Name: LOIMPR, where LOIMPR=Yes, and LOI date variable = LOIMDAT).

The number of “responders” will be presented as frequency counts and percentages by treatment arm. The primary efficacy analysis will test the hypothesis of equal response rates using Barnard’s Unconditional Exact Test as implemented in the EXACT statement of PROC FREQ in SAS 9.4, with rows corresponding to treatment arms and columns corresponding to binomial response indicators. An exact confidence interval for the difference in response rates will be computed using the RISKDIFF(METHOD=SCORE) option. In addition, exact

confidence intervals will be provided for each treatment's response rate based on the Clopper-Pearson method.

Similar analysis will be conducted on the ITT population as a sensitivity analysis.

8.8.2 Secondary Efficacy Endpoints

- The percentage of SLE patients without loss of disease activity improvement from Day 1 to Day 169 (i.e., responders) will be evaluated as described in the primary endpoint analysis (above) on both the efficacy evaluable and ITT populations (sensitivity).
- The time to loss of SLE disease activity improvement achieved by a short period of IM steroid therapy in SLE patients. The time to loss of SLE disease activity improvement will be calculated from date of randomization to the date loss of improvement is first achieved. This endpoint will be summarized by treatment arm using Kaplan-Meier methods (median, 95% CI, number of events, number censored, etc.) and Kaplan-Meier plots. The log-rank test will be used to test for treatment group differences. Similar analysis will be conducted on the ITT population as a sensitivity analysis.

Patients who discontinue treatment early will be censored at their last assessment date that occurred within 4 weeks of their final dose, whichever comes first. Patients who complete the study with no observed LOI will be censored at day 225.

- Multivariate analysis: Cox proportional hazards regression will be used to explore the potential effects of pre-specified prognostic factors on time to loss of SLE disease activity improvement. The adjusted hazard ratios for treatment versus placebo and covariates will be estimated, together with 95% CIs. A pre-specified analysis will employ a forward, then backward stepwise approach. In the forward step, prognostic factors will be added in the order specified below in Section 8.8.2.1 (excepting those for which other handling is described for the factor), with retention of those factors for which the Wald test $P \leq 0.10$. After all factors have been tested individually in sequential order, the resulting multivariate model will be evaluated with a backwards stepwise procedure. Those factors with $P > 0.20$ in the full model will be removed in order of largest p-value until all final factors have $P \leq 0.20$. This final model will be summarized in a table and a forest plot. The analysis will be performed on the ITT population only. Patients who discontinue treatment early will be censored at their last assessment date that occurred within 4 weeks of their final dose. Patients who complete the study with no observed LOI will be censored at Day 225. Additional exploratory multivariate proportional hazards

analyses may be performed, for example, to assess treatment effect modification by subgroups (i.e. modeled either as post-hoc stratifications or interactions).

8.8.2.1 Pre-specified Prognostic Factors

- 1) BILAG Total Score at screening and change in BILAG total score from Screening visit to Day 1 dosing visit. Stepwise procedures will test these two factors together using a likelihood ratio test instead of individually using Wald tests.
- 2) BILAG number of A and B scores at screening and change in number of A and B scores from Screening visit to Day 1 dosing visit. Stepwise procedures will test these two factors together using a likelihood ratio test instead of individually using Wald tests.
- 3) SELENA SLEDAI Score at screening and change in SELENA SLEDAI Score from Screening visit to Day 1 dosing visit. Stepwise procedures will test these two factors together using a likelihood ratio test instead of individually using Wald tests.
- 4) Physician's Global Disease activity VAS at screening and change in the VAS from Screening visit to Day 1 dosing visit. Stepwise procedures will test these two factors together using a likelihood ratio test instead of individually using Wald tests.
- 5) Total Depomedrol dose, including screening doses and Day 1 and 15 doses
- 6) Daily Prednisone dose at Day 1
- 7) FcγRIIa R131H Polymorphism
- 8) FcγRIIb I232T Polymorphism
- 9) BMI at baseline
- 10) Study day of first noncompliant steroid use at any time on study prior to LOI (i.e. time-varying covariate), as assessed by the Sponsor's medical monitor. Patients in this group may also be excluded from an exploratory sensitivity analysis or, alternatively, censored at the date of first noncompliant steroid use.
- 11) Study day of any non-protocol SLE therapy in the absence of an earlier LOI determination. Patients with non-missing values for this factor will be evaluated for informative censoring in a sensitivity analysis using a proportional hazards model with censoring times replaced by LOI events at the start of non-protocol therapy. This analysis may not be reported in the CSR if the treatment effect estimate changes less than 10% and statistical significance conclusions are unaffected.

8.8.3 Exploratory Efficacy Endpoints

The following disease assessment indices will be used for exploratory analyses of disease activity over time:

- Physician's Global Assessment (PGA) VAS
- SELENA SLEDAI hybrid version with SELENA SLEDAI Flare index
- BILAG 2004

The PGA, SLEDAI, and BILAG will be summarized by treatment arm at each visit using descriptive statistics (N, mean, standard deviation, median, minimum/maximum). Change from baseline will also be tabulated at each visit using the same descriptive statistics. Categorical variables will be presented as frequency counts and percentages. These exploratory endpoints will be evaluated on both the efficacy evaluable and ITT populations (sensitivity).

8.9 Safety Analysis

Safety Population is defined as all patients who received at least a partial dose of XmAb5871 or Placebo and will be utilized for all safety analyses. In this study the Safety Population is equivalent to the ITT population.

8.9.1 Treatment Emergent Adverse Events

All AEs reported before a patient's first dose will be reported as non-treatment adverse events in patient listings. All medications taken since the time of first dose until the end of the study will be classified as TEAEs.

All Treatment Emergent Adverse Events (TEAEs) will be listed, documenting all information collected on the eCRF.

Verbatim terms of TEAEs will be mapped to preferred terms and related system organ classes (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.0.

Tables will summarize the number and percentage of patients having a TEAE in each system organ class and preferred term. Further tables will summarize the number and percentage of patients having TEAE, classified according event intensity (severity graded 1-5 according to CTCAE v4.03) and the number and percentage of patients with "related" events.

- *'Related' includes events where the relationship to the study drug was reported as 'Possibly Related', 'Probably Related', and 'Definitively Related' or where the relationship was not reported on the CRF.*
- *'Not Related' are events reported as 'Not Related' and 'Unlikely Related' on the CRF.*

The order of SOCs presented in tables will be according to the internationally agreed order of SOCs according to MedDRA. Within each SOC, the preferred terms will be shown in alphabetic order.

Note: Patients who have multiple events in the same SOC and/or preferred term will be counted only once at each level of summation (overall, by SOC, and by preferred term) in the tables. For summaries of AEs by severity, only the highest severity of AE will be counted at each level of summation (overall, by SOC, and by preferred term) in the tables. For summaries of related AEs, patients with more than one related AE will be counted only once at each level of summation (overall, by SOC, and by preferred term) in the tables.

8.9.2 Serious Adverse Events

A listing of patients who reported a serious adverse event will be included. The data will be obtained from the AE dataset where the AESAE=Yes for that specific adverse event.

8.9.3 Adverse Events Leading to Discontinuation from Study

A listing of patients and the adverse events which led to study discontinuation from the study will be included. The data will be obtained from the AE dataset where AEDISC=Yes.

Additionally, AEs will be identified from the EOS dataset where the primary reason for treatment termination is checked as an Adverse Event. These two datasets will be reconciled prior to database lock.

8.9.4 Deaths

A listing of patients who died on study will be included. Any associated AE will be identified from the AE dataset where AEDEATH box is checked.

8.9.5 Clinical Laboratory Tests

Hematology: The following hematology parameters will be assessed at Screening and at Days 1, 8, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, 169, 183, 197, 211, 225 and 253 (EOS): hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (% and derived absolute values), mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and absolute platelet count.

Clinical chemistry: The following clinical chemistry parameters will be assessed at Screening and at Days 1, 8, 29, 57, 85, 113, 141, 169, 197, 225 and 253 (EOS): total protein, sodium, potassium, calcium, chloride, bicarbonate (HCO₃), inorganic phosphate, albumin, glucose, blood urea nitrogen (BUN), creatinine, uric acid, bilirubin, alkaline phosphatase (AP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), creatine phosphokinase (CPK), amylase, and lipase.

Urinalysis: The following urinalysis parameters will be assessed at Screening, and on Days 1, 29, 57, 85, 113, 141, 169, 197, 225, and 253 (EOS): pH, glucose, ketones, specific gravity, nitrite, protein, bilirubin, urobilinogen, leukocytes and blood. Microscopic urinalysis will be performed if urinalysis results are abnormal. A spot urine protein/creatinine ratio will be performed for urine dipstick of 2+ or greater protein.

Coagulation: The following coagulation parameters will be assessed on Screening, and Days 1, 29, 85, 141, 197, and 253 (EOS): international normalized ratio (INR), prothrombin time (PT), and activated partial thromboplastin time (aPTT).

Immunoglobulin: Serum IgG, IgE, and IgM will be assessed at Screening and on Days 1, 15, 71, 127, 155, 183, 211, and 253 (EOS).

Complement levels: C3 and C4 levels will be assessed at Screening and on Days 1, 29, 57, 85, 113, 141, 169, 197, 225, and 253 (EOS).

Shift tables (shift from baseline grade to maximum (and minimum) post-dose grade) will be presented for chemistry, hematology, and coagulation tests.

Summary statistics (n, mean, SD, min, max) will be utilized to characterize immunoglobulins and complement levels and will be presented by Visit and Timepoint. Corresponding change from baseline and percent change from baseline will also be presented for immunoglobulins and complement levels

Urinalysis parameters will be presented in patient listings.

The results from urine Pregnancy tests (Screening, Days 1, 15, 43, 71, 99, 127, 155, 183, 211, and 253), Follicle Stimulating Hormone (assessed at Screening only), and Serology (assessed at Screening only: HBsAg, HBcAb, and HCV Ab) will be presented in patient listings.

Individual patient data listings of all chemistry, hematology, coagulation, urinalysis, serum immunoglobulins and complement (C3 and C4) results will be presented by patient and time point.

All values outside the clinical reference ranges will be flagged in the data listings. The abnormal values will be flagged with 'Low' for values below the lower limit of the clinical reference range and 'High' for values above the upper limit of the clinical reference range and included in the listings. The investigator or designee will assess whether the values outside the clinical reference range are clinically significant and these will be reported as abnormal not clinically significant (NCS) or abnormal clinically significant (CS). Clinically significant laboratory and that are not explained by the patient's underlying disease or medications should be entered as AEs and the relationship to study drug assigned. Additional testing during the study may be done if medically indicated. The study patient will be followed until the test(s) has (have) normalized or stabilized.

8.9.6 Vital Signs

Vital signs will be assessed at Screening and on Days 1, 8, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, 169, 183, 197, 211, 225, and 253 (EOS). On Day 1, vital sign assessments will be made immediately prior to infusion, 15, 30, 60, and 120 minutes after the start of the infusion (± 5 minutes), immediately before the EOI (if different than 120 minutes from start of infusion), and at 15, 30, 60 and 120 minutes after EOI. During subsequent infusions, vital signs will be measured immediately prior to infusion, 30 and 60 minutes after the start of the infusion (± 5 minutes), immediately before the EOI (if different than 60 minutes from start of infusion), and at 30 and 60 minutes after EOI. On non-dosing days vital signs should be measured prior to blood sampling. During the infusion of XmAb5871, vital signs will be obtained in the semi-supine sitting position. The following vital signs will be measured:

- Blood pressure (systolic and diastolic [mmHg]);
- Heart rate (beats per minute [bpm]);
- Oral body temperature ($^{\circ}\text{C}$);
- Respiratory rate (breaths per minute).
- Supine BP and heart rate recordings will be made after the study patient has been recumbent and at rest ≥ 5 minutes.

Vital sign variables will be summarized in a descriptive manner by calculating the observed mean, standard deviation, median, and range at baseline and at each post-baseline measurement. Mean change and mean percent change from baseline will also be presented.

All vital sign tests will be included in by-patient listings for further medical review.

8.9.7 12-Lead Electrocardiogram

Standard safety 12-lead ECGs will be performed at Screening and on Days 1, 29, 127, 183, and 253 (EOS). On Day 1, supine ECGs will be performed immediately prior to the infusion and 2 hours after EOI. On all other visit days, ECGs will be performed only pre-dose.

The 12-lead ECGs will be performed after the patient has been resting supine for ≥ 5 minutes. The following ECG parameters will be collected: PR interval, QRS interval, RR interval, QT interval, and QTc interval (QTcB and QTcF).

Each ECG parameter will be summarized in a descriptive manner by calculating the observed mean, standard deviation, median, and range at baseline and at each post-baseline measurement. Mean change and mean percent change from baseline will also be presented.

QTcB and QTcF values will be categorized according to their values into the categories

- ≤ 430 ms
- 430 – 450 ms
- 450 – 480 ms
- 480 – 500 ms
- 500 ms

and categorized according to their change from baseline into the categories

- ≤ 30 ms,
- 30 – 60 ms
- 60 ms

The categories described above will be summarized in frequency tables using number of patients (n) and percentages.

All ECGs must be evaluated by a qualified physician for the presence of abnormalities.

8.10 Pharmacokinetics (PK)

XmAb5871 pharmacokinetic visit, scheduled time point, sampling dates/times will be listed by patient. The individual patient pre-dose (trough) and end-of-infusion (peak) concentration-time data will be listed and displayed graphically on the linear and log scales. The concentration-time data will be summarized descriptively in tabular and graphical formats (linear and log scales).

PK data analysis will be undertaken by a PK consultant.

8.11 Pharmacodynamics (PD)

All observed Pharmacodynamics data collection date/times will be provided in patient listings.

PD of XmAb5871 will be evaluated by absolute B cell counts (ABC) and B cell subsets, and CD19 receptor occupancy (RO).

Flow Cytometry B Cell and T Cell Assessment:

- CD20+ B cells and T cells will be quantified at Screening and on Days 1, 8, 15, 29, 57, 85, 113, 141, 169, 197, 225, and 253 (EOS).
- CD19 RO (as CD19+ geometric mean of all CD20+ [MFI]) and B cell subsets (CD20+, CD20+/IgD+CD27-, CD20+/IgD+CD27+, CD20+/IgD-CD27+-, CD20+/IgD-CD27-) will be quantified at Screening and on Days 1, 8, 15, 29, 57, 85, 113, 141, 169, 197, 225, and 253 (EOS).

All observed PD data and change from baseline data will be summarized using descriptive statistics and will be listed and summarized in tabular and/or graphical form. Descriptive statistics on continuous data will include mean, median, standard deviation, and range, while categorical data may be summarized using frequency counts and percentages.

PD data will be analyzed by an appropriate expert consultant in this field.

8.12 Pharmacokinetic/Pharmacodynamic Analyses

Individual and mean peak and trough serum concentrations of XmAb5871 will be summarized in tabular form and plotted versus time on dual y-axis plots along with biomarkers CD19 RO and ABC % change from baseline.

The peak and trough serum concentrations of XmAb5871 will be examined by FcγRIIa R131H and FcγRIIb I232T polymorphisms to determine if these genetic characteristics affect pharmacokinetics.

8.13 Immunogenicity: Human Anti-Human Antibodies (AHA)

The presence of human anti-human antibodies (ADA) will be assessed on Days 1, 15, 43, 85, 127, 183, 225, and 253 (EOS). Frequency and titer of anti-XmAb5871 antibodies (ADA) will be listed.

8.14 Pharmacogenomics

The date/time (if not done, reason why) and result of the pharmacogenomics evaluation (FcγR genotype testing: FcγRIIa R131H and FcγRIIb I232T polymorphisms) will be listed

by patient. Polymorphism frequencies will be tabulated along with the baseline characteristics.

Where patients provided informed consent, the residual Fc γ R polymorphism sample was retained by Xencor or Xencor's designee for future exploratory genotyping research. Samples are to be maintained for no more than 15 years before destruction. Samples are to be stored at Cancer Genetics Inc.

9. INTERIM ANALYSIS

No formal efficacy interim analyses are planned; however aggregate blinded interim safety reviews will be performed for submission to regulatory authorities. The blinded aggregate safety information will be reviewed by a Safety Review Committee (SRC) after 15 patients have completed the study, after 45 patients have completed the study, and after 75 patients have completed the study. The SRC will consist of, at a minimum, the coordinating investigator and the medical representatives of the Sponsor (Xencor) and the CRO (PPD). The principal investigators and/or their delegates from each actively enrolling investigational site will be allowed to participate. All patients in the study will receive appropriate SLE rescue therapy at the discretion of the principal investigator and discontinue study drug infusions at the time of loss of disease activity improvement, however the SRC may request an unblinded review of safety data by an independent review committee should there be a trend in either an increase frequency of early SLE disease flares or the occurrence of organ-threatening SLE disease flares.

A Safety Review Charter will be developed and implemented prior to the first safety review meeting.

10. TESTING/VALIDATION PLAN AND SOFTWARE SYSTEM

Statistical Analysis Software (SAS) version 9.4 or later will be used to analyze the data, create summary tables, patient data listings, and graphical representation of the data. All SAS programs will be validated using industry standard validation procedures.

11. STATISTICAL ANALYSIS CHANGES FROM THE PROTOCOL

The analyses described are based on the final clinical study protocol XmAb5871-04 Version 2.0 dated July 29, 2016. This SAP supersedes the statistical considerations identified in the protocol. Note the following differences between this SAP version and the Protocol:

- 1) Since PK sampling is limited to peak and trough samples, PK reporting will be limited to serum concentration listings, summary descriptive statistics over time and mean peak and trough figures over time, as specified in this SAP. Expert analysis of PK data, such as non-compartmental analyses, will not be performed due to the limited peak and trough sampling scheme.
- 2) Since PK sampling is limited to peak and trough samples, the PK population will be defined more simply to include ‘all patients with at least one pre-dose and one post-dose evaluable result reported.’
- 3) PK/PD comparisons will be limited figures comparing mean peak and trough concentrations to CD19RO and ABC % change from baseline.
- 4) Components of the mechanistic studies exploratory endpoints and all mechanistic study analyses may be reported separately from the main clinical study report. These analyses are not detailed in this SAP.

12. REFERENCES

1. Protocol XmAb5871-04: A Randomized, Double-Blinded, Placebo-Controlled Study of the Effect of XmAb®5871 on Systemic Lupus Erythematosus Disease Activity. Version 2.0, July 29, 2016.
2. International Federation of Pharmaceutical Manufacturers and Associations. Medical Dictionary for Regulatory Activities (MedDRA). Version 19.0 Reston, Virginia, USA; 2008.
3. WHO Collaborating Center for International Drug Monitoring. WHO Drug Dictionary. WHO Drug version 201509. Uppsala, Sweden; 2008.
4. SAS Institute Inc. SAS Version 9.3. Cary, NC, USA; 2002-2003.
5. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.
6. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.

13. SCHEDULE OF ASSESSMENTS

Study Phase	SCR	Treatment													
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Study Week	-4	1	2	3	5	7	9	11	13	15	17	19	21	23	
Study Day	-28 to -1	1	8 +/-1	15 +/- 1	29 +/- 1	43 +/- 1	57 +/- 1	71 +/- 1	85 +/- 1	99 +/- 2	113 +/-2	127 +/-2	141 +/-2	155 +/- 2	
Informed consent	X														
Withdraw immuno-suppressant	X ^(c)														
Depomedrol IM	X ^(d)	X		X											
Improvement assessment		X													
Study drug administration		X		X	X	X	X	X	X	X	X	X	X	X	
AE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Medical history	X	X													
Physical exam	X	X	X		X		X		X		X		X		
Vital signs ^(e)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Electrocardiogram (ECG)	X	X ^(f)			X							X			
CBC, differential, platelets	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry panel	X	X	X		X		X		X		X		X		
PT/INR and APTT	X	X			X				X				X		
Urinalysis	X	X			X		X		X		X		X		
HBsAg, HCV Ab, HBc Ab	X														
Pregnancy test ^(g)	X	X		X		X		X		X		X		X	
FSH ^(h)	X														
FcγR polymorphisms ⁽ⁱ⁾		X													
T and B cell enumeration, CD19RO and B cell subsets	X	X	X	X	X		X		X		X		X		
SELENA SLEDAI	X	X			X		X		X		X		X		
BILAG 2004	X	X			X		X		X		X		X		
SLE Autoantibody Panel	X	X			X		X		X		X		X		
C3 and C4	X	X			X		X		X		X		X		
PGA	X	X			X		X		X		X		X		
Serum IgM, IgG, IgE	X	X		X				X				X		X	
PK blood ^(j)		X	X	X	X		X		X		X		X	X	
Immunogenicity (ADA) ^(k)		X		X		X			X			X			
Mechanistic studies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Study Phase						EOS
Visit Number	15	16	17	18	19 ^[b]	20 ^[b]
Study Week	25	27	29	31	33 ^[b]	37 ^[b]
Study Day	169 +/-2	183 +/-2	197 +/-2	211 +/-2	225 ^[b] +/-3	253 ^[b] +/-3
Informed consent						
Withdraw immuno-suppressant						
Depomedrol IM						
Improvement assessment						
Study drug administration	X	X	X	X		
AE Assessment	X	X	X	X	X	X
Medical history						
Physical exam	X		X		X	X
Vital signs ^[e]	X	X	X	X	X	X
Electrocardiogram (ECG)		X				X
CBC, differential, platelets	X	X	X	X	X	X
Chemistry panel	X		X		X	X
PT/INR and APTT			X			X
Urinalysis	X		X		X	X
HBsAg, HCV Ab, HBc Ab						
Pregnancy test ^[g]		X		X		X
FSH ^[h]						
FcyR polymorphisms ^[i]						
T and B cell enumeration, CD19RO and B cell subsets	X		X		X	X
SELENA SLEDAI	X		X		X	X
BILAG 2004	X		X		X	X
SLE Autoantibody Panel	X		X		X	X
C3 and C4	X		X		X	X
PGA	X		X		X	X
Serum IgM, IgG, IgE		X		X		X
PK blood ^[j]	X		X	X	X	X
Immunogenicity (ADA) ^[k]		X			X	X
Mechanistic studies	X	X	X	X	X	X

^[a] Unless otherwise stated, assessments should be performed pre-dose.

^[b] If a patient experiences a loss of disease activity improvement (LOI), they will receive no more infusions of study drug. Assessments listed above under Day 225 should be performed at the time of loss of disease activity improvement and assessments for Day 253 (EOS) should be performed at a visit 6 weeks from the time of the last study drug infusion.

^[c] Immunosuppressants may be discontinued anytime from screening start but before Day 1. During screening, investigators may give additional steroids IM up to 320 mg total at their discretion to achieve the targeted disease improvement.

^[d] Patients receive 160 mg depomedrol IM at the beginning of screening and may receive up to additional 320 mg during screening to suppress disease activity at the principal investigator's discretion. All patients will receive 80 mg of IM depomedrol on Days 1 and 15.

^[e] On Day 1, vital sign assessments will be made immediately prior to infusion, 15, 30, 60, and 120 minutes after the start of the infusion (±5 minutes), immediately before the EOI (if different than 120 minutes from start of infusion), and at 15, 30, 60 and 120 minutes after EOI. During subsequent infusions, vital signs will be measured immediately prior to infusion, 30 and 60 minutes after the start of the infusion (±5 minutes), immediately before the EOI (if different than 60 minutes from start of infusion), and at 30 and 60 minutes after EOI.

^[f] On Day 1, supine ECGs will be performed immediately prior to the infusion and 2 hours after EOI. On all other visit days, ECGs will be performed only pre-dose.

^[g] Pregnancy test only for women of child-bearing potential

^[h] FSH only in women of non-childbearing potential

^[i] Sample to be taken pre-dose.

^[j] PK blood at trough levels prior to infusion and at end of infusion

^[k] ADA sample should be drawn at the time of any suspected immunological related AE and at the time of each subsequent visit X 4.

APPENDIX 1. IMPUTATION OF PARTIAL AND MISSING DATES

Adverse Event

All AE onset dates must be entered on the eCRF as complete dates. In the rare case that all or part of an AE onset date is missing but an AE resolution date is present and after first dose date then the AE onset date will be imputed as follows:

Year of onset	Month of onset	Day of onset	Onset date to be imputed as
Missing	Missing	Missing	Date of first dose
year = year of first dose	Missing	Non-missing	Set month to month of first dose
year = year of first dose	Missing	Missing	Set month and day to those of first dose
year < year of first dose	Missing	Non-missing	set month to December
year < year of first dose	Missing	Missing	set month and day to December 31
year > year of first dose	Missing	Non-missing	set month to January
year > year of first dose	Missing	Missing	set month and day to January 1
year = year of first dose	Month = month of first dose	Missing	Set day as day of 1st dose
year = year of first dose	Month < month of first dose	Missing	Set day as last day of onset month
year = year of first dose	Month > month of first dose	Missing	Set day as first day of onset month
year < year of first dose	Non-missing	Missing	Set day as last day of onset month
year > year of first dose	Non-missing	Missing	Set day as first day of onset month

If AE resolution date is present and prior to first dose date, then there is no need to impute incomplete AE start date, as the AE is not treatment emergent and the event should be in the medical history.

Concomitant Medications

- If year and month are present and day is missing then set day to first day of month for start date, and set day to last day of month for end date
- If year and day are present and month is missing then set month to January for start date, and set month to December for end date
- If year is present and month and day are missing then set month and day to January 1 for start date, and set month and day to December 31 for end date
- Completely missing dates will not be imputed
- If start date is completely missing and end date is on or after the first dose, then the medication will be classified as concomitant; if the end date is missing, then the medication will be classified as ongoing. Medications for which the start and end dates are completely missing will be classified as concomitant.

Medical History and Diagnosis Dates

- If day is missing and month is non-missing, day will be set to 15th of the month.
- If month is missing and day is non-missing, then month will be set to July.
- If month and day are both missing, month and day will be set to July 1st.
- If complete date is missing, then impute it as the date of informed consent -1.