Clinical Study Protocol

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

Sponsor:	Xencor, Inc. 111 West Lemon Avenue Monrovia, CA 91016
Clinical Research Organization:	Pharmaceutical Product Development, LLC 929 N Front St Wilmington, NC 28401
Coordinating Investigator:	Joan T. Merrill, MD
Sponsor Protocol No.:	XmAb5871-04
IND No.:	125,319
IMP Name:	XmAb5871
Development Phase:	Phase 2
Version, Date:	Version 2.0 Amendment 1 29 July 2016

This clinical study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP) as outlined in CPMP/ICH/135/95, with the Declaration of Helsinki (Version 2008) and with other applicable regulatory requirements.

SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Expert

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

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal product (IMP), as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (Version 2008), and the current guidelines on Good Clinical Practices (GCP) applicable to this clinical study.

Sponsor Signatory/Responsible Medical Expert

Debra Zack, MD, PhD
Vice President, Clinical Development
Xencor, Inc.

29 July 2016
Date

SIGNATURE PAGE

Declaration of the Principal Investigator

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

This clinical study protocol was subjected to critical review and has been released by the Sponsor. I have read this protocol and agree that the information it contains is consistent with current risk and benefit evaluation of the investigational medicinal product (IMP), as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (Version 2008), and the current guidelines on Good Clinical Practices (GCP) applicable to this clinical study.

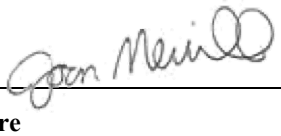
I will provide copies of the protocol and of the clinical and preclinical information on the investigational product, which was furnished to me by the Sponsor, to all members of the study team responsible to me who participate in the study. I will discuss this material with them to assure that they are fully informed regarding the study drug and the conduct of the study.

I will perform the study according to specifications outlined in the protocol and agree to implement protocol requirements only after this protocol version and the patient information/informed consent forms have been approved by the Institutional Review Board (IRB). I will not modify this protocol without obtaining the prior approval of the Sponsor and of the IRB. I will submit any protocol modifications (amendments) and/or any informed consent form modifications to the Sponsor and the IRB, and approval will be obtained before any modifications are implemented.

I understand that the information presented in this study protocol is confidential, and I hereby assure that no information based on the conduct of the study will be released without prior consent from the Sponsor Xencor, Inc., unless this requirement is superseded by a regulatory authority, e.g., FDA.

I agree to conduct the study as outlined in this Clinical Study Protocol dated 27 July 2016. Any modification of the Clinical Study Protocol must be agreed upon by the Sponsor and the Investigator(s) and must be documented in writing.

Principal Investigator



August 2, 2016
Signature / **Date**
Joan T. Merrill, M.D.	Oklahoma Medical Research Foundation
Printed name / **Institution**

PROTOCOL SYNOPSIS

Protocol Title:	A Randomized, Double-Blinded, Placebo-Controlled Study of the Effect of XmAb®5871 on Systemic Lupus Erythematosus Disease Activity
Protocol Short Title	Phase 2 Study of XmAb5871 in Patients with SLE
Study Number:	Sponsor Protocol No.: XmAb5871-04
Investigational Product	XmAb®5871
IND Number	125,319
Development Phase:	Phase 2
Indication	Systemic Lupus Erythematosus (SLE)
Sponsor:	Xencor, Inc.
Coordinating Investigator:	Joan T. Merrill, MD
Study Center(s):	Up to 25 sites

Study Objectives:	**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
	Secondary Objective
	• 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
	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

Study Design:	This is a randomized double-blind, placebo-controlled study of approximately 90 patients with SLE. Participants will receive 5 mg/kg XmAb5871 or placebo (randomized 1:1) by IV infusion every other week for up to a total of 16 infusions.
Investigational Medicinal Product(s); IMP, Dose and Route of Administration:	XmAb5871 drug product is a liquid product supplied in single-use glass vials. Each 10 mL glass vial is filled with 10.5 mL of drug product containing 10.0 (+/- 5%) mg/mL of XmAb5871, 10 mM sodium phosphate, 150 mM sodium chloride and 0.01% (w/v) polysorbate 20 at pH 7.2. Dose and route of administration: Every other week administration of XmAb5871 at 5.0 mg/kg by IV infusion over 1-2 hours Placebo to match XmAb5871, administered by IV infusion over 1-2 hours
Number of Patients:	Approximately 90 patients with active SLE

Study Population:	Male and female patients ages 18 to 65 inclusive with active SLE at screening
Study Duration	After up to a 4-week screening period, participants will receive XmAb5871 or placebo IV 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 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.
Criteria for Evaluation:	**Disease Activity:** The following disease activity parameters will be recorded at scheduled intervals throughout the study: • SELENA SLEDAI using the SELENA SLEDAI hybrid version with the SELENA SLEDAI Flare Index • BILAG using the BILAG 2004 • Physician's Global Assessment VAS **Safety:** The following safety parameters will be recorded at regular intervals during the study: • Adverse events (CTCAE v 4.03) • Vital signs (supine blood pressure [BP], heart rate [HR], oral body temperature, respiratory rate [RR]) • Twelve-lead electrocardiogram (ECG) • Clinical laboratory testing (clinical chemistry, hematology, coagulation and urinalysis) • Serum immunoglobulin (Ig) levels (IgG, IgM, IgE) • B cell and T cell quantification by flow cytometry • Concomitant medications • Physical examinations **Immunogenicity:** The following immunogenicity parameter will be recorded during the study: • Anti-XmAb5871 antibodies (anti-drug antibodies [ADA]) **Pharmacokinetics:** Serum XmAb5871 peak and trough serum concentrations will be measured in this study. **Pharmacodynamics:** • Circulating ABC count • SLE autoantibody panel, complement levels and cytokine profile **Pharmacogenomics:** • FcγRIIa R131H polymorphism • FcγRIIb I232T polymorphism
Statistical Methods:	<u>Sample size considerations:</u> Sample size is based on a previously completed study of SLE patients treated with disease-suppressing IM depomedrol therapy for up to 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 placebo response of 10% and a 38% XmAb5871 response in preventing loss of disease activity improvement, the number of patients needed for 80% power and 5% significance would be approximately 40 per arm. Adding approximately 10% for unevaluable patients, the total number per arm is calculated as 45. Statistics: Summary statistics for continuous variables will include the mean, standard deviation, median and range (minimum/maximum). Categorical variables will be presented as frequency counts and percentages; and time-to-event variables will be summarized using Kaplan-Meier methods (median, 95% CI, number of events, number censored, Kaplan-Meier figures). Data listings will be created to support each table and to present all data. The primary efficacy endpoint will be evaluated as the percentage of patients without loss of disease activity improvement on Day 225. The percentage of patients without loss of disease activity improvement on Day 169 will be a secondary endpoint. Loss of improvement (LOI) will be defined as worsening of disease activity that: In the opinion of the principal investigator requires change in treatment (exclusive of a decrease in oral steroid use) AND one of 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) A new BILAG A or B score. The Fishers exact test will be performed on the Efficacy Evaluable Population to test for treatment group differences. The same analysis on the ITT Population will also be utilized for sensitivity analysis. In addition to the percentage of patients without loss of disease activity improvement on Day 169, the time to loss of SLE disease activity improvement achieved by a short period of IM steroid therapy in SLE patients will be a secondary endpoint. 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 on the Efficacy Evaluable and ITT populations. All safety data will be based on the Safety Population. The number and percent of patients experiencing a treatment-emergent adverse event will be tabulated for each coded MedDRA system-organ class and preferred term by treatment arm. Treatment-emergent adverse events will also be tabulated according to intensity and causality by treatment arm. Clinical laboratory tests, vital signs, and ECG data will be summarized by treatment arm using descriptive statistics.

LIST OF STUDY STAFF

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Immunogenicity (ADA) Assessment Laboratory:	Mallika Kopalle ICON Laboratory Services, Inc. 8282 Halsey Road Whitesboro, NY 13492 Telephone number: 315-768-2834

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Clinical Laboratory (including Flow Cytometry B- and T-cell Assessment Laboratory):	Alisa Euler ICON Laboratory Services, Inc. 123 Smith Street Farmingdale, NY 11735 Telephone number: 631-306-9676 Email: Alisa.euler@iconplc.com
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LIST OF ABBREVIATIONS

Abbreviation	Definition
Ab	Antibody
ADA	Antidrug antibody
AE	Adverse event
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	The area under the serum concentration-time curve from time zero to time point at a later time x (AUC_x), time point of the last measurable concentration (AUC_{last}), or extrapolated to time infinity (AUC_∞)
BCR	B cell receptor
BILAG	British Isles Lupus Activity Group, in this protocol, version BILAG2004
BP	Blood pressure
bpm	Beats per minute
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulations
CL	Clearance of drug
C_{last}	Last measurable concentration
C_{max}	Maximum observed concentration
CPK	Creatine phosphokinase
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
D5W	5% dextrose
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbant assay
EOI	End of infusion
EOS	End-of-study
Fc	Fragment, crystallizable
FcγRIIb	Fcγ receptor IIb
FDA	Food and Drug Administration

FIH	First in human
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GLP	Good Laboratory Practice
H	Histidine
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HCO_3	Bicarbonate
HCV	Hepatitis C virus
IB	Investigator's Brochure
IC	Immune complex
IC_{50}	Median inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFNγ	Interferon gamma
Ig	Immunoglobulin
IL-4	Interleukin-4
IMP	Investigational medicinal product
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IU	International units
IUD	Intrauterine device
IV	Intravenous
k_D	Dissociation constant
LDH	Lactate dehydrogenase
LOI	Loss of disease activity improvement
mAb	Monoclonal antibody
mmHg	Millimeters of mercury
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NIAID	National Institute of Allergy and Infectious Diseases

NK	Natural killer
NOAEL	No observable adverse effect level
NSAID	Nonsteroidal anti-inflammatory drug
OTC	Over-the-counter
PBMC	Peripheral blood mononuclear cell
PD	Pharmacodynamic
PEF	Peak expiratory flow
PI	Principal investigator
PK	Pharmacokinetic
PT	Prothrombin time
R	Arginine
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SCID	Severe combined immunodeficiency
SD	Standard deviation
SELENA SLEDAI	SLE disease activity index as modified in the SELENA study
SID	Subject identification
SOP	Standard Operating Procedure
$T_{1/2}$	Terminal phase half-life of drug
TEAE	Treatment-emergent adverse event
TNFα	Tumor necrosis factor alpha
ULN	Upper limit of normal
URI	Upper respiratory infection

PROTOCOL NO. XmAb5871-04AMENDMENT 1 - 27 JULY 2016

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

SUMMARY OF CHANGES – VERSION 1 TO VERSION 2

Page	Section	Change (bolded text added; strikethrough text deleted)	Justification
4	Protocol Synopsis (Study Design)	**Changed the following stricken text and added the following bold text:** *Participants will receive 5 mg/kg XmAb5871 or placebo (randomized 1:1) by IV infusion every other week for up to a total of **16** ~~12~~ infusions.*	• Adding 4 additional infusions for a total of 16
5	Protocol Synopsis (Study Duration)	**Changed the following stricken text and added the following bold text:** *After up to a 4-week screening period, participants will receive XmAb5871 or placebo IV every other week for up to a total of **16**~~12~~ doses (**30**~~22~~ weeks) and will be followed for 6 weeks following the last dose for a total study period of up to **40**~~32~~ weeks.*	• Incorporating the additional 8 weeks of dosing
5-6	Protocol Synopsis (Study Procedures)	**Changed the following stricken text and added the following bold text:** *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**~~155~~ for a total of up to **16** ~~12~~ infusions.* *Patients will return on study Days 29, 43, 57, 71, 85, 99, 113, 127, 141, ~~and~~ 155, **169, 183, 197 and 211** for XmAb5871 or placebo administration IV over 1-2 hours and for safety, PK and PD assessments.* *Patients who meet the criteria for loss of disease activity improvement at any timepoint up to and including Day **211**~~155~~ will not receive further infusions of XmAb5871 or placebo* *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**~~169~~ **(primary endpoint) and Day 169 (secondary endpoint).** Patients with loss of disease activity*	• Incorporating the additional 8 weeks of dosing • The new primary endpoint will be at 2 weeks after the last infusion, with the previous Day 169 evaluation becoming a secondary endpoint.

Page	Section	Change (bolded text added; strikethrough text deleted)	Justification
		*improvement at any time-point up to and including Day **225**~~169~~ will be considered non-responders for the primary endpoint.* *All patients completing the treatment period should be followed through Day **253**~~197~~(EOS).*	
7	Protocol Synopsis (Statistical Methods)	**Changed the following stricken text and added the following bold text:** *The primary efficacy endpoint will be evaluated as the percentage of patients without loss of disease activity improvement on Day **225** ~~169~~. **The percentage of patients without loss of disease activity improvement on Day 169 will be a secondary endpoint.*** ***In addition to the percentage of patients without loss of disease activity improvement on Day 169,** ~~. The secondary efficacy endpoint will beof~~ the time to loss of SLE disease activity improvement achieved by a short period of IM steroid therapy in SLE patients **will be a secondary endpoint. This endpoint** will be summarized by treatment arm using Kaplan-Meier methods*	• Adjusts the primary endpoint to Day 225, with percentage of patients without loss of disease activity improvement on Day 169 made a secondary endpoint.
8	List of Study Staff (Contract Research Organization)	**Updated the name and contact information for the following staff:** ***Justine Bucholz*** ~~*Cherie Young*~~ *PPD* ***3900 Paramount Parkway*** ~~*929 N Front St*~~ ***Morrisville***~~*Wilmington*~~*, NC **27560-7200**~~*28401*~~ *Telephone number: **910-558-4994*** ***Cell: 234-788-3475*** ~~*512 284 4927*~~ *Email: **Justine.Bucholz@ppdi.com*** ~~*Cherie.Young@ppdi.com*~~	• Updated to reflect personnel changes
8	List of Study Staff (Bioanalytical Laboratory – PK)	**Updated the name and contact information for the following staff:** ~~*Deborah P. Candido*~~ ***Cynthia Wydysh*** *ICON **Laboratory Services, Inc.*** ~~*Development Solutions, LLC*~~ *8282 Halsey Road* *Whitesboro, NY 13492* *Telephone number: **315-768-2527***	• Updated to reflect personnel and address changes

Page	Section	Change (bolded text added; strikethrough text deleted)	Justification
		Fax number: 315-736-2460 *Email:* ***Cynthia.Wydysh@iconplc.com*** ~~*Telephone number: 315-768-2554*~~ ~~*Email: Deborah.Candido@iconplc.com*~~	
8	List of Study Staff (Genotyping Laboratory)	**Updated the name of the Genotyping Laboratory:** *Ryan Newman* ***Cancer Genetics, Inc.***~~*Gentris Corporation*~~ *133 Southcenter Court, Suite 400* *Morrisville, NC 27560* *Telephone number: 919-653-5532* *Fax number: 919-653-5542* *Email: Ryan.Newman@****cgix.***~~*Gentris.*~~*com*	• Updated to reflect changed company name and emails
8-9	List of Study Staff (Immunogenicity Laboratory – ADA)	**Updated the name and contact information for the following staff:** ~~*Melissa Mitchell*~~ ***Mallika Kopalle*** *ICON* ***Laboratory Services, Inc.*** ~~*Development Solutions, LLC*~~ *8282 Halsey Road* *Whitesboro, NY 13492* ***Telephone number: 315-768-2834*** ~~*Telephone number: 315-768-2800*~~ *Email:* ~~*Melissa.Mitchell*~~ ***Mallika.Kopalle@iconplc.com***	• Updated to reflect personnel and address changes
9	List of Study Staff (Clinical Laboratory including Flow Lab)	**Updated the name and contact information for the following staff:** *Alisa Euler* *ICON* ***Laboratory Services, Inc****.* ~~*Central Laboratory*~~	• Updated to reflect address changes
37-39	3.1 Overall Study Design and Plan	**Added the following bolded text and deleted the stricken text:** *All patients will receive 5.0 mg/kg of XmAb5871 or matched placebo over 1-2 hours IV on an every other week dosing schedule for a total of*	• Extending the number of infusions to 16 and updating the visit dates accordingly.

Page	Section	Change (bolded text added; strikethrough text deleted)	Justification
		*up to **16** ~~12~~ doses.* *Those patients who achieve the required disease activity improvement from the screening baseline will be randomized to receive either XmAb5871 (5 mg/kg) or placebo by IV administration (double-blinded) over 1-2 hours every 2 weeks from Day 1 through Day **211**~~155~~ for a total of up to **16** ~~12~~ infusions.* *On Day 15 and on study Days 29, 43, 57, 71, 85, 99, 113, 127, 141, ~~and~~ 155, **169, 183, 197, and 211** patients will return for XmAb5871 (5 mg/kg) or placebo administration IV over 1-2 hour* *Patients who meet the criteria for loss of disease activity improvement at any timepoint up to and including Day **211**~~155~~ will not receive further infusions of XmAb5871 or placebo* *Patients who discontinue the study early either because of loss of improvement or for other reasons will be followed for safety for a further period of 6 weeks after their last dose of XmAb5871 or placebo (completing assessments in schedule of events listed as Day **225**~~169~~ as the LOI visit and Day **253**~~197~~[EOS] visit 4 weeks later) at which time their participation is completed.* *All patients completing the treatment period should be followed through Day **253**~~197~~(EOS).* *The effect of XmAb5871 on maintenance of improvement of SLE disease activity will be evaluated as the percentage of patients without loss of improvement at Day **225**~~169~~ **(primary endpoint) and Day 169 (secondary endpoint).***	• Updating primary endpoint to 2 weeks after final infusion and adding the Day 169 (after 12 infusions) efficacy evaluation as previously planned as a secondary endpoint.
39	3.2 Discussion of Study Design	**Added the following bolded text:** ***The protocol has been amended to change the time of the primary endpoint from 6 months to 8 months to account for the more prolonged initial course of IM steroid therapy being given in this study relative to the BOLD study.***	• Explanation for the addition of 4 more infusions and longer time to primary endpoint.
40	3.4.1 Disease Activity	**Added the following bolded text and deleted the stricken text:** *The primary endpoint will be evaluated as the percentage of patients without loss of disease activity improvement at Day **253**~~169~~. **The percentage of patients without loss of disease activity improvement on Day 169 and** ~~T~~time to loss of disease activity improvement will be*	• Updated to reflect longer dosing period.

Page	Section	Change (bolded text added; strikethrough text deleted)	Justification
		*evaluated as ~~a~~ secondary endpoint**s**.*	
40	3.4.2 Mechanistic Studies	**Added the following bolded text and deleted the stricken text:** *Blood will be collected and analyzed at Screening, Day 1, Day 29 and either at the first visit with loss of disease activity improvement (LOI) or 2 weeks after the last infusion (Day **225**~~169~~), whichever comes first.*	• Updated to reflect longer dosing period.
42	3.5 Stopping Criteria for the Clinical Study	**Added the following bolded text and deleted the stricken text:** *The Investigator will make all appropriate safety assessments on an ongoing basis. The Sponsor's medical representative will review individual safety information as it becomes available throughout the study. In addition, **un**blinded aggregate safety information will be reviewed by ~~the~~ **an external** Safety Review Committee (SRC) after **approximately** 15 patients have completed the study, **and** after **approximately** 45 ~~patients have completed the study, and after~~**and** 75 patients have completed the study. The SRC will consist of, at a minimum**, two rheumatologists with SLE expertise and a biostatistician who will review the data in an unblinded manner. T**~~t~~he coordinating investigator and the medical representatives of the Sponsor (Xencor) and the CRO (PPD) **will review blinded data only.** ~~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 blinded study team may request an unblinded review of safety data by the SRCan independent review committee should there be a trend in either an increased frequency of early SLE disease flares or the occurrence of organ-threatening SLE disease flares.~~*	• Updated to reflect the addition of an unblinded external safety committee.

Page	Section	Change (bolded text added; strikethrough text deleted)	Justification
44	4.2 Inclusion Criteria	**Added the following bolded text:** *3. Patients have a history of a (+) ANA, (+) ENA **(anti-RNP or anti-Smith)** or a (+) anti-dsDNA serology documented by laboratory report within the year prior to randomization.*	• *Clarification of ENA for sites*
47	4.4 Patient Withdrawal and Replacement	**Added the following bolded text and deleted the stricken text:** *At the time that a patient withdrawals prematurely for any reason, all assessments as listed for the Day **225**~~169~~ visit should be performed. In addition, the patient should be scheduled for a follow-up visit 6 weeks from the time of the last infusion of study drug, at which time all assessments as listed for the Day **253**~~197~~ (EOS) visit should be performed.*	• Changed to reflect longer trial period
52	5.8 Administration of Investigational Medicinal Product	**Added the following bolded text:** ***For the initial infusion,** p~~P~~atients are to remain fasted for at least 3 hours before starting the infusion until at least 1 hour after end of infusion. During pre-infusion fasting, no fluids are allowed except small amounts of water. During the post-dose fasting period, small amounts of clear liquids will be allowed. **At subsequent infusions, patients should fast for 1 hour prior, may have clear liquids during and after the infusion, and may resume their normal diet 1 hour later.***	• Fasting periods have been relaxed following the first infusion since the infusion-related gastrointestinal symptoms occur primarily during the first infusion.
62	6.1.2.3.6 Adverse Events of Special Interest (Management of Infusion-Related Reactions & Cytokine Release Syndrome)	**Added the following bolded text:** ***An ADA sample should be drawn at the time of any suspected immunological related AE and at the time of each subsequent visit X 4 (and as per pre-specified sampling schedule).***	• Added as per FDA's request in the comments on the IND filing
66	6.1.2.4 Reporting of Serious Adverse Events	**Added the following bolded text and deleted the stricken text:** *SERIOUS ADVERSE EVENT REPORTING INSTRUCTIONS* ***SAEXmAb5871-04@vigilareintl.com***	• Update to reflect updated SAE reporting procedure

Page	Section	Change (bolded text added; strikethrough text deleted)	Justification
		24 hour telephone number: 610-977-0899 x4801 *Emergency contact number: 917-741-5205* ~~*Portal url: https://vigilareintl.sharepoint.com/xencor*~~ *1.* ***E-mail your SAE form to the study specific e-mail address above.*** ~~*Telephone Vigilare to state that you are forwarding an SAE form. If Vigilare is not available, leave a message in the voice mailbox, and call the emergency contact number*~~*.*	
67	6.1.2.6 Pregnancy	**Added the following bolded text:** *Each pregnancy notification must be reported by the Investigator to the Sponsor and Vigilare within 30 days after becoming aware of the pregnancy.* ***In the event of pregnancy in a female participant, no more study drug will be given. However, t****~~T~~he Investigator must follow-up*	• Clarification that in the event of a patient's pregnancy, no further drug should be given.
67	6.1.3 Vital Signs	**Added the following bolded text and deleted the stricken text:** *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***~~*197*~~ *(EOS).*	• Addition of extra infusion days
68	6.1.4 12-lead Electrocardiograms	**Added the following bolded text and deleted the stricken text:** *Standard safety 12-lead ECGs will be performed at Screening and on Days 1, 29, 127,* ***183,*** *and* ***253***~~*197*~~ *(EOS).*	• Addition of extra infusion days
68	6.1.5 Physical Examinations	**Added the following bolded text and deleted the stricken text:** *Physical examinations will be performed at Screening and on Days 1, 8, 29, 57, 85, 113, 141, 169,* ~~*and*~~ *197****, 225 and 253*** *(EOS).*	• Update to account for additional infusions
68-70	6.1.6 Clinical Laboratory Assessments	**Added the following bolded text and deleted the stricken text:** *Genotyping will be performed by* ***Cancer Genetics Inc.***~~*Gentris*~~*, Morrisville, NC.* *•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***~~*197*~~*(EOS)* *•Clinical chemistry: The following clinical chemistry parameters will be assessed at Screening and at Day 1, 8, 29, 57, 85, 113, 141, 169,*	• Company has changed its name. • Updated all assessments to add additional visit dates

Page	Section	Change (bolded text added; strikethrough text deleted)	Justification
		~~and~~ *197,* ***225 and 253****(EOS)* *•Immunoglobulin: Serum IgG, IgE, and IgM will be assessed at Screening and on Days 1, 15, 71, 127, 155,* ***183, 211 and 253***~~*197*~~*(EOS).* *•Complement levels: C3 and C4 levels will be assessed at Screening and on Days 1, 29, 57, 85, 113, 141, 169,* ~~and~~ *197,* ***225 and 253****(EOS).* *•Coagulation: The following coagulation parameters will be assessed on Screening, and Days 1, 29, 85, 141,* ~~and~~ *197* ***and 253****(EOS)* *•Urinalysis: The following urinalysis parameters will be assessed at Screening, and on Days 1, 29, 57, 85, 113, 141, 169,* ~~and~~ *197,* ***225 and 253****(EOS)* *•Urine pregnancy test: Urine pregnancy testing will be performed in female patients at Screening, Days 1, 15, 43, 71, 99, 127, 155,* ***183, 211 and 253***~~*197*~~*(EOS).* *•Immunogenicity: The presence of human anti-human antibodies (ADA) will be assessed on Days 1, 15, 43, 85, 127, 183*~~*69*~~*,* ***225 and 253***~~*197*~~*(EOS).* *•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,* ~~and~~ *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,* ~~and~~ *197,* ***225 and 253****(EOS).* *Mechanistic studies:* *For randomized patients, mechanistic studies that will be performed on Days 1, 29, and at the LOI visit (either at the visit at which loss of response is noted or on Day* ***225***~~*169*~~ *Additional samples will be collected at screening and on Days 8, 15, 57, 71, 99, 113, 127, 141, 155,* ~~and~~ ***169, 183, 197, 211 and 253*** ~~*197*~~ *(or EOS 6 weeks after loss of improvement, whichever comes first) and stored for potential mechanistic studies. Screening samples for all*	• Requirements for the RNA PAX gene tubes are 7 mL instead of 18 mL. Clarification of type of PAX gene tube.

Page	Section	Change (bolded text added; strikethrough text deleted)	Justification
		*patients will be analyzed for ANA with pattern and anticardiolipin antibodies, with a repeat anticardiolipin antibody panel at LOI or Day **225**~~169~~, whichever comes first.* *Blood requirements* *•Mechanistic Studies: Blood (**25**~~36~~ mL) will be collected into one 10 mL SST tube, one 10 mL green top (heparin) tube and 2 **RNA** PAX gene tubes.*	
72	6.2 Pharmacokinetic Variables	**Added the following bolded text and deleted the stricken text:** *prior to the start of the infusion and at EOI on Study Days 1, 15, 29, 57, 85, 113, 141, and 155 and at visit time on Days 8, **225**~~169~~ and **253**~~197~~(EOS).*	• Correction for addition of extra infusion days
72	6.4 Pharmacogenomics Variables	**Added the following bolded text and deleted the stricken text:** ***Cancer Genetics Inc***.~~*Gentris Corporation*~~	• Correction to updated company name
72	6.4.1 Efficacy Measurements	**Added the following bolded text and deleted the stricken text:** *Disease activity will be measured at Screening and on Days 1, 29, 57, 85, 113, 141, 169, ~~and~~ 197, **225 and 253** (EOS).*	• Addition of measurements to account for extra infusion days
74	7.1 Schedule of Assessments	**Added the following bolded text and deleted the stricken text:** *The study consists of a Screening visit (Day -28 to Day -1) followed by ~~twelve~~ **sixteen** infusions of XmAb5871 given every two weeks (Days 1, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, ~~and~~ 155, **169, 183, 197 and 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**~~169~~ and **253**~~197~~[EOS]).* *Assessments listed for the Day **225**~~169~~ visit should be performed at the time of loss of disease activity improvement (LOI). Assessments listed for the Day **253**~~197~~(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**~~197~~ days after the first infusion.*	• Corrections to account for increase in number of infusions
74	7.1.2 Early Termination	**Added the following bolded text and deleted the stricken text:** *If a patient withdraws prematurely after dosing, assessments listed for*	• Updated to account for increase in length of study

<table>
<tr><th>Page</th><th>Section</th><th>Change (bolded text added; strikethrough text deleted)</th><th>Justification</th></tr>
<tr><td></td><td>Visit</td><td>the Day 225<s>169</s> visit should be performed at the time of loss of disease activity improvement or time of discontinuation for other reasons. Assessments listed for the Day 253<s>197</s>(EOS) visit should be performed at the follow-up visit 6 weeks from the time of the last study drug infusion as a final safety check.</td><td></td></tr>
<tr><td>74</td><td>7.1.3 End-of-Study</td><td>The following bolded text has been added and stricken text deleted:
End-of-Study is defined as completion of the End-of Study Visit on Day 253<s>197</s>.</td><td>• Updated to account for increase in study duration.</td></tr>
<tr><td>75</td><td>Table 6: Schedule of Assessments</td><td>The following bolded text has been added:
Study Day 8 +/-1
Immunogenicity (ADA) [k,l]</td><td>• Windows for Day 8 added (correction)
• Footnotes for followup of positive ADA added</td></tr>
<tr><td>76</td><td>Table 6: Schedule of Assessments</td><td>The following addition to Table 6 has been added:</td><td>• Addition of 4 extra infusion days with accompanying safety and efficacy labs and assessments</td></tr>
<tr><td></td><td></td><td>
<table>
<tr><th>Study Phase</th><th colspan="5"></th><th>EOS</th></tr>
<tr><th>Visit Number</th><th>15</th><th>16</th><th>17</th><th>18</th><th>19[b]</th><th>20[b]</th></tr>
<tr><th>Study Week</th><th>25</th><th>27</th><th>29</th><th>31</th><th>33[b]</th><th>37[b]</th></tr>
<tr><th>Study Day</th><th>169
+/-2</th><th>183
+/-2</th><th>197
+/-2</th><th>211
+/-2</th><th>225[b]
+/-3</th><th>253[b]
+/-3</th></tr>
<tr><td>Informed consent</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Withdraw immuno-suppressant</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Depomedrol IM</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Improvement</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
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Page	Section	Change (bolded text added; strikethrough text deleted)	Justification

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]							
FcγR polymorphisms[i]							
T and B cell	X		X		X	X	

<table>
<tr><th>Page</th><th>Section</th><th>Change (bolded text added; strikethrough text deleted)</th><th>Justification</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>enumeration, CD19RO and B cell subsets</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>SELENA SLEDAI</td><td>X</td><td></td><td>X</td><td></td><td>X</td><td>X</td></tr>
<tr><td>BILAG 2004</td><td>X</td><td></td><td>X</td><td></td><td>X</td><td>X</td></tr>
<tr><td>SLE Autoantibody Panel</td><td>X</td><td></td><td>X</td><td></td><td>X</td><td>X</td></tr>
<tr><td>C3 and C4</td><td>X</td><td></td><td>X</td><td></td><td>X</td><td>X</td></tr>
<tr><td>PGA</td><td>X</td><td></td><td>X</td><td></td><td>X</td><td>X</td></tr>
<tr><td>Serum IgM, IgG, IgE</td><td></td><td>X</td><td></td><td>X</td><td></td><td>X</td></tr>
<tr><td>PK blood[j]</td><td>X</td><td></td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>Immunogenicity (ADA) [k]</td><td></td><td>X</td><td></td><td></td><td>X</td><td>X</td></tr>
<tr><td>Mechanistic studies</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
</table>
</td><td></td></tr>
<tr><td>77</td><td>Table 6: Schedule of Assessments</td><td>The following bolded text has been added and stricken text deleted in the footnotes of Table 6:
[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 ~~169~~ 225 should be performed at the time of loss of disease activity improvement and assessments for Day 253~~197~~ (EOS) should be performed at a visit 6 weeks from the time of the last study drug 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.</td><td>• Updated to account for longer study duration
• Aligns Table 6 with the previous section changes</td></tr>
</table>

Page	Section	Change (bolded text added; strikethrough text deleted)	Justification
78	8.1.3 Analysis Populations	**Added the following bolded text and deleted the stricken text:** •*Efficacy Evaluable Population: All patients who:* *Complete study through Day **225~~169~~** assessments*	• Correction for addition of study days
81	8.6.1 Primary Efficacy Endpoint	**Added the following bolded text and deleted the stricken text:** *(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~~169~~** (i.e., responders).* *The primary efficacy analysis will employ the Fisher's Exact Test testing for differences in treatment response rate (patients without loss of disease activity improvement from Day 1 to Day **225~~169~~**) between the two treatment groups.*	• Clarification of dates • Correction for addition of study days
81	8.6.2 Secondary Efficacy Endpoint	**Added the following bolded text and deleted the stricken text:** *8.6.2Secondary Efficacy Endpoint**s** ~~(Time to Loss of Improvement)~~* ***The percentage of SLE patients without loss of disease activity improvement from Day 1 to Day 169 (i.e., responders) will be evaluated as above.***	• Addition of another secondary endpoint
		Add BOLD reference if available	

1. INTRODUCTION

1.1. Background

1.1.1. Role of B Cells in Autoimmunity

Autoimmune diseases, including connective tissue diseases and bullous diseases, confer high risk of chronic symptoms, poor quality of life and progressive disability, and may be life-threatening. Recent clinical and experimental approaches have demonstrated that B cells play critical roles in the pathophysiology of autoimmune disease. They do so not only by well-established autoantibody-mediated mechanisms but also by a variety of other functions including interactions with dendritic cells and T cells. B cell activation and autoantibody production therefore offer an important therapeutic target mechanism for the management of immune-mediated conditions. B cell directed therapies are approved for both the treatment of rheumatoid arthritis (RA) (rituximab) and systemic lupus erythematosis (SLE) (belimumab).

B cells are activated through a number of cell surface receptors including the B cell receptor (BCR). The BCR, once coupled with cognate antigen, induces a complex signaling pathway that results in B cell activation, proliferation and differentiation. The BCR response to antigen is modulated by a number of specialized cell surface co-receptors, or response regulators, which inform B cells of their microenvironment. These response regulators include cluster of differentiation 19 (CD19) and CD22. In addition, B cells have Fcγ receptor IIb (FcγRIIb) on their surface. Activation of FcγRIIb results in down-regulation of BCR signaling and decreased B cell function. FcγRIIb has also been shown to play a crucial role in suppressing autoimmunity (Nimmerjahn et al 2008, McGaha et al 2005, Tarasenko et al 2007, Brownlie et al 2008).

1.1.2. XmAb5871

XmAb®5871 is a humanized monoclonal antibody (mAb) being developed by Xencor Inc. for the treatment of B cell mediated autoimmune disorders such as SLE, RA and IgG4 Related Disease (IgG4-RD).

XmAb5871 is a humanized Fc (fragment, crystallizable) engineered mAb that binds to the human B cell restricted surface antigen CD19 and has enhanced Fc binding to FcγRIIb. The antibody variable region of XmAb5871 has been engineered to increase affinity to human CD19, while the constant region is engineered to increase affinity for the inhibitory FcγRIIb (Chu et al 2008, Horton et al 2011).

FcγRIIb is the only Fc receptor (FcR) on B cells and serves as an antibody-sensing down-regulator of humoral immunity that is naturally engaged by immune complexes (Smith et al 2010). When sufficient antibody is raised against a given antigen, specific immune complexes form and co-engage FcγRIIb and the BCR with high avidity, selectively suppressing only B cells that recognize cognate antigen. In addition, FcγRIIb regulates the activity of other B cell stimulators including IL-4, lipopolysaccharide (LPS), and B cell activating factor (BAFF) that amplify BCR-driven B cell proliferation and differentiation (Crowley et al 2009).

By simultaneously binding CD19 and FcγRIIb, XmAb5871 mimics the action of antigen-antibody complexes and down-regulates B cell activity. The proposed mechanism of action of XmAb5871 of simultaneously binding CD19 and FcγRIIb and down regulating B cell activity has been demonstrated in vitro and in vivo, including inhibition of peripheral B cells from SLE patients (Horton et al 2011) and in classical animal models of autoimmune disease.

1.1.3. Systemic Lupus Erythematosus (SLE)

SLE is the prototypic autoimmune disease, with many immunological abnormalities including the presence of a plethora of autoantibodies, hyperactive B cells, activated T cells, increased cytokines and increased innate immune function. Hyperactive B cells may play a role both as the precursors to autoantibody-producing cells and as antigen presenting cells to other cells of the immune system such as T cells. Autoantibodies complexed with their autoantigens stimulate plasmacytoid dendritic cells and neutrophils. Several groups have shown down-regulation of the inhibitory Fc receptor, FcγRIIb, in mouse models of SLE and on memory B cells and plasmablasts from SLE patients. This correlated with a decreased suppression of BCR induced responses in those B cells and suggested that a critical checkpoint in memory B cell regulation, FcγRIIb, might be impaired (Mackay et al 2006, Su et al 2007). Therefore, targeting this receptor to restore a more normal level of suppressive function could potentially help to reduce the activation of the immune system in SLE.

SLE is a chronic systemic autoimmune disease that may affect multiple organs. The ACR Classification criteria for SLE (Tan et al, 1982) include malar rash, discoid rash, photosensitivity, arthritis, serositis, renal disorder, neurologic disorder, hematologic disorder, immunologic disorder (autoantibodies), and antinuclear antibody (ANA), of which any 4 of the 11 can be present to classify a patient as having SLE. SLE is typically a disease of young women ages 15-45, with a 10-fold greater incidence in women than in men. There are some ethnic differences, with greater prevalence and severity of disease in persons of African, Hispanic, Asian and Native American descent. While the risk of mortality has decreased to 5-10% at 10 years, patients still die of active disease, infection, cardiovascular causes, and

treatment associated effects. Despite improved survival, it is estimated that only 15% of patients have good to excellent disease control sustained for 1 year (http://www.niams.nih.gov/Health_Info/Lupus/default.asp).

The frequent remissions and flares that characterize the disease have made development of assessment tools and the design of clinical studies difficult. The confounding effects of concomitant medications have often been considered to be a major reason for the inability to show efficacy of potential new therapeutics (Bruce et al 2010, Thanou et al 2014). Trial designs other than the frequently utilized model of adding a new drug or placebo on top of standard of care have been needed. Recently, a Biomarker of Lupus Disease study (BOLD, NCT 00987831) was completed at Oklahoma Medical Research Foundation that used a design that, by reducing potential for placebo response, could allow proof-of-concept for new therapeutic agents with enrollment of a much smaller number of patients. Forty-one SLE patients with active, non-organ threatening disease had a brief course of IM depomedrol substituted for their ineffective SLE medications. All achieved disease activity improvement following 1-4 injections of 160 mg of IM depomedrol given over 2 weeks, with 360 mg the mean amount of steroid given. The investigator then monitored the patients until they required additional therapy for loss of disease activity improvement. Forty of the 41 required the addition of other therapy within 6 months with the overall median time to loss of disease activity improvement of 56 days. This suggested that the effect of the brief course of IM depomedrol therapy gradually wore off over the first few months. The patients received rescue therapy as soon as disease activity improvement was lost and there was a quick response to rescue therapy. There were no SAEs from disease flares and patients did not have disease flares of manifestations that were worse than their previous disease activity (Merrill et al 2011). In addition, a predictive model using biomarkers of disease (Guthridge et al 2014) indicated the likelihood of an early flare was drastically reduced in the absence of activated monocytes (activated $CD11b^{hi}$) and activated naïve B cells ($CD86^{hi}$). Conclusions from the study were that patients with moderately severe, non-organ threatening SLE can tolerate withdrawal of their ineffective treatments for periods of time and that their disease activity can be controlled with a short period of IM steroid therapy. The design was thought to reflect clinical practice and to support a trial design with disease amelioration (steroids) at baseline and immediate treatment if disease activity returns (Merrill 2013). Therefore, this design has the potential to study investigational agents that could be added at the time of improvement with IM steroid therapy. An effective agent would be expected to reduce the number of patients who would require additional therapy, and should be able to do so within a reasonably short period of study time (6 months). Using the BOLD study design, the present study proposes to test if XmAb5871 can improve on the proportion of patients at 6 months that

maintain disease activity improvement induced by IM steroid therapy after ineffective (and potentially confounding) agents are discontinued. This is particularly interesting given the demonstrated ability of XmAb5871 to suppress the expression of CD86 on stimulated SLE and normal human B cells.

1.1.4. Current Treatment of SLE

SLE is currently incurable. The goals of treatment are to reduce inflammation and damage to the organs and to prevent or reverse disease exacerbations. Therapy is tailored to the organ systems involved and the amount of inflammation, but most of the agents used are non-specific immunosuppressants that are frequently used in combination. For milder forms of SLE involving skin and/or joints, topical or low dose oral steroids, hydroxychloroquine, NSAIDs and/or methotrexate are often the mainstay of therapy. Involvement of other organ systems often warrants higher doses of oral steroids together with agents such as azathioprine, mycophenolate mofetil, or belimumab.

Aggressive treatment is warranted when vital organs are involved to prevent organ damage or failure. High dose oral or IV corticosteroids with cyclophosphamide, azathioprine, or mycophenolate mofetil may be used for organ threatening disease in the kidneys, CVS, and hematopoetic systems. Many of the therapeutics are less than optimal therapies particularly for young women because of their long term safety profiles. For example, long term corticosteroid use can lead to hypertension, diabetes, osteoporosis, and infection risk, whereas cyclophosphamide may lead to sterility and bladder cancer. Only one new therapy for SLE, belimumab, has been approved in over 50 years.

Therefore, there is a need for more targeted agents to control the disease long-term. Because of the presumed role of B cells in SLE, the effect of a B cell inhibitor might provide a more long-term solution to disease control.

1.2. Non-Clinical Studies

1.2.1. Pharmacology of XmAb5871

1.2.1.1. In Vitro Pharmacology

XmAb5871 has two key functional attributes; binding to human CD19 (hCD19) and binding to human FcγRIIb. The EC_{50} of binding of XmAb5871 to an hCD19 expressing cell line (Ramos) is 0.3 nM. The EC_{50} of binding to human primary B cells is 1.4 nM when measured under similar assay conditions. Human B cells express both CD19 and FcγRIIb, so the EC_{50} of 1.4 nM represents the avidity of XmAb5871 for the human B cell surface. The affinity of XmAb5871 to cynomolgus monkey (the relevant toxicology species) CD19 is approximately 6 fold lower than

its affinity for human CD19. No appreciable XmAb5871 binding was detected with B cells from mouse, rat, rabbit, or dog.

The second functional attribute important for the pharmacology of XmAb5871 is the enhanced binding to FcγRIIb relative to binding to other FcγRs. FcγRs, expressed on a wide variety of immune cells, bind to the Fc portion of immunoglobulin G (IgG) to mediate a range of immunological functions. FcγRI (CD64), FcγRIIa (CD32a), and FcγRIIIa (CD16a) are all activating receptors that signal through the intracellular immunoreceptor, known as tyrosine based activation motif (ITAM). In contrast, FcγRIIb (CD32b) signals via the immunoreceptor tyrosine based inhibitory motif (ITIM) leading to the down-regulation of immune responses.

The affinity of XmAb5871 for human FcγRIIb is approximately 8 nM, representing an increase of approximately 225-fold relative to human native IgG1. The binding affinity of XmAb5871 for the human activating FcγRs is reduced or unchanged except for one allele of a commonly occurring polymorphism in FcγRIIa, the R131 allele. The affinity of XmAb5871 for the R131 allele of the activating receptor FcγRIIa (~3 nM) is increased over 150-fold relative to native IgG1. In contrast, a slight decrease in affinity was observed for the H131 allele of FcγRIIa, implicating the arginine at position 131 as a key amino acid residue for the capacity of the XmAb5871 Fc to bind to FcγRIIb with increased affinity. FcγRIIb contains an arginine residue at the analogous amino acid position and there are no known polymorphisms at this amino acid position in human FcγRIIb.

The binding affinities of XmAb5871 to activating FcγRs in human and cynomolgus monkey were similar. However, the significant increase in affinity for the human inhibitory receptor FcγRIIb was not observed with the analogous cynomolgus monkey inhibitory receptor FcγRIIb (250 fold less). This is probably due to the absence of an arginine amino acid residue at position 131 in the FcγRIIb of cynomolgus monkey.

XmAb5871 inhibits B cell activation by binding to CD19 and FcγRIIb simultaneously. The co-engagement of these 2 receptors is the presumed mechanism by which excess antigen-antibody complexes down-regulate B cell activity. In vitro co-engagement of CD19 and FcγRIIb by XmAb5871 was shown to inhibit BCR induced calcium release in human B cells. The effect is dependent on both CD19 and FcγRIIb binding and cannot be mimicked by control antibodies that bind to only one of these targets or the other. Similarly, control antibodies directed against the two targets individually are ineffective in down-regulating B cell activity, even if such antibodies were used in combination.

Because FcγRIIb has been shown to be dysregulated in SLE patients (Mackay et al, 2006), B cells from SLE donors were studied in vitro to determine whether they would respond to XmAb5871 in a similar fashion to normal healthy volunteers. As with the normal B cells, XmAb5871 was able to stimulate FcγRIIb and suppress BCR-induced calcium mobilization, B cell proliferation and expression of costimulatory molecules (CD86) on SLE-derived B cells. In addition, B cell proliferation induced by any of the B cell stimuli LPS, IL-4, and BAFF was suppressed by XmAb5871 in SLE B cells, just as in normal (Horton et al 2011). This suggests that even though SLE patients may have less expression of FcγRIIb, their cells are still able to respond to XmAb5871.

1.2.1.2. In Vivo Pharmacology

In vivo, XmAb5871 inhibits human B cell function in a model of human peripheral blood mononuclear cell (PBMC) xenografts in severe combined immunodeficient (SCID) mice. In these studies, engrafted human B cell response to an in vivo tetanus toxoid antigen challenge can be blocked by XmAb5871. Tetanus toxoid-specific human IgG production was inhibited by XmAb5871, whereas negative control antibodies (e.g., those that bind human CD19 but not human FcγRIIb) did not differ from buffer alone. These studies show an inhibitory effect on specific B cell activation by XmAb5871.

A murine pharmacology model was also developed in which the murine Fc receptor gene was removed and the human FcγRIIb gene inserted. These transgenic mice were then used to demonstrate the protective effect of a surrogate antibody that recognizes human FcγRIIb and murine CD19 in a collagen-induced arthritis (CIA) model of polyarticular disease. Treatment with the surrogate antibody successfully blocked both the incidence and severity of the disease (for more details, see Investigator Brochure).

1.2.2. Secondary Pharmacology: Off Target Receptor Binding Studies

Although the binding affinity of XmAb5871 for FcγRIIb is approximately 225 fold increased, the binding affinity to the activating receptor FcγRIIIa, involved in antibody-dependent cell-mediated cytotoxicity (ADCC) by NK cells, was reduced approximately 20-fold relative to native human IgG1 Fc (Chu et al 2008). ADCC-mediated killing of B cells is an important mechanism of depletion of mature B cell populations in humans by the anti-CD20 mAb rituximab (Reff et al 1994). In ex vivo human PBMC cultures, XmAb5871 did not stimulate B cell depletion, while 2 known depleting antibodies, rituximab (anti-CD20; Reff et al 1994) and XmAb5574 (an anti-CD19 antibody with the Fc engineered to enhance FcγRIIIa binding; Horton et al 2008) depleted B cells in a dose-dependent manner.

FcγRIIa, a low affinity, activating FcγR present on human platelets and myeloid cells (monocytes, dendritic cells, macrophages), is important in macrophage mediated antibody-dependent cell-mediated phagocytosis (ADCP). Two alleles of the gene encoding FcγRIIa generate 2 variants differing at amino acid position 131. The histidine (H131) and arginine (R131) alleles are reported to be roughly equally distributed with some ethnic variation. The affinity of XmAb5871 for FcγRIIa R131 is increased 150-fold relative to that of wild type IgG1 binding, but the affinity for the H131 allotype is slightly decreased relative to IgG1. Potential implications of this increased binding to FcγRIIa R131 (i.e., ADCP) were examined in vitro. In vitro phagocytosis experiments demonstrate that monocyte-derived macrophages from R131 positive donors will, in the presence of XmAb5871, phagocytose Ramos cells ($CD19^+$ B cell line) and purified human B cells. Very little phagocytosis was observed with monocyte-derived macrophages from H131 homozygous donors, but these observations raise the possibility of B cell reduction or depletion in R131 positive patients. However, neither data from the first-in-human (FIH) study in healthy volunteers nor data from the multiple ascending dose study in RA patients have shown an association of the presence of the R131 allele with the extent of B cell count reduction following dosing with XmAb5871.

In the human FcγRIIb transgenic mouse model, a surrogate antibody that recognizes human FcγRIIb and murine CD19 did not cause B cell depletion. A small reduction in B cell count was observed possibly due to inhibition of BCR-mediated proliferation signals. Interestingly, the surrogate antibody did produce B cell depletion in the same strain of mice lacking the human FcγRIIb transgene, suggesting that the presence of human FcγRIIb may be protective against B cell depletion mediated by activating FcRs.

FcγRIIa is the sole FcγR expressed on human platelets. Cross-linking of FcγRIIa by platelet-antigen associated immune complexes has been demonstrated to fully activate platelets for secretion and aggregation. While neither CD19 nor FcγRIIb are platelet-associated antigens, the potential for platelet interaction was evaluated. In an ex vivo study, the addition of XmAb5871 to samples from human donors did not induce platelet activation. Additionally, in the completed human studies in healthy subjects and in RA patients, no changes in platelet count were observed.

Whole blood assays were also used to monitor for possible cytokine release in response to XmAb5871. No XmAb5871-mediated release of TNF-α or interferon γ (IFN-γ) was observed. In the completed FIH single ascending dose study, there were no signs or symptoms consistent with cytokine release syndrome or immunologically mediated infusion-related reactions. In the Phase 2a study in RA patients, two of 40 patients (5%) experienced an infusion-related reaction

with hypotension, both at a dose of 10.0 mg/kg. One occurred at the time of the first infusion and the other during the second infusion. It is possible the infusion-related reactions were mediated by cytokine release.

1.2.3. Nonclinical Pharmacokinetics and Toxicology of XmAb5871

The cynomolgus monkey was found to be the single most relevant common toxicology species based on flow cytometric analysis of XmAb5871 binding to lymphocytes from different species. XmAb5871 cross reacted with B cells from cynomolgus monkey but failed to bind to cells from mouse, rat, rabbit or dog. Human and cynomolgus monkey binding affinities were similar for most of the FcγRs, however, the binding affinity to FcγRIIb of the cynomolgus monkey was approximately 250-fold less strong than that observed for the corresponding human receptor. However ex vivo studies have confirmed that FcγRIIb was engaged by XmAb5871 on cynomolgus monkey B cells and was capable of inducing pharmacologically measurable consequences despite the 250-fold lower FcγRIIb binding affinity.

1.2.3.1. Tissue Cross-Reactivity Studies

The CD19 antigen is restricted to B cell lineages (Nadler et al 1983, Meeker et al 1984). In a cross-reactivity study with a normal human tissue panel, fluorescein-XmAb5871 stained mononuclear leukocytes and lymphocytes which were judged to be B cells based on their morphology and/or localization. Some staining (weak to moderate) was noted in a variety of human cell types which are presumed not to express CD19. The staining in these tissues was often observable only at the higher concentration of antibody tested and not observed in the analogous monkey tissues. The tissues include Kupffer cells and endothelium of the liver. Endothelium, Hofbauer cells and spindloid cells of placental sections and spindloid cells and Leydig cells of the testes showed weak to moderate staining.

A companion study with cynomolgus monkey tissues also stained mononuclear leukocytes and lymphocytes and bone marrow precursor cells judged to be of B cell origin. No other binding was observed in the monkey tissues.

1.2.3.2. Non-GLP and GLP Toxicology Studies in Cynomolgus Monkey

In an exploratory non-good laboratory practice (GLP) PK/toxicity study in 12 cynomolgus monkeys (two/gender/group), XmAb5871 or vehicle was administered as a single 1 hour IV infusion at doses of 3 or 30 mg/kg. Necropsies were performed in 6 monkeys (1 of each sex per group) on study days 30 and 92. There were no mortalities and single IV administration of XmAb5871 in cynomolgus monkey was tolerated well at both 3 and 30 mg/kg. There were no test article-related changes identified in clinical observations, food consumption, body weights, hematology, serum chemistry, gross or microscopic anatomical pathology parameters.

A GLP 12-week repeat-dose toxicity study was completed in cynomolgus monkeys of both genders. XmAb5871 was administered via a one hour IV infusion at doses of 0, 2, 10 or 50 mg/kg on an every other week × 6 dosing regimen. Exposure of cynomolgus monkeys to 6 administrations of XmAb5871 at 14-day intervals was well-tolerated, with all animals surviving to scheduled sacrifice. No test article-related changes were observed in clinical observations, food consumption, body weight, electrocardiography, ophthalmology, hematology, serum chemistry, coagulation, urinalysis, organ weight, gross observations, or histopathology.

Dose-dependent decreases in the mean absolute and relative B cell (CD3-CD20+) counts were observed, relative to baseline levels, on Days 15 and 43; however, recovery of B cell counts to at least 75% of baseline occurred during the dosing period for all groups. The reduction in B cell count to less than 75% of baseline levels (Day -1) did not occur at any time during dosing for the 2 mg/kg and 10 mg/kg groups. In the 50 mg/kg group, the B cell count was reduced to approximately 45% of baseline on Day 15 (pre-dose infusion #2) and Day 43 (pre-dose infusion #4) and recovered to within 75% of baseline counts on Day 71 (pre-dose infusion #6). No test article-effects were noted in T lymphocyte counts or total lymphocyte counts, and no microscopic changes were observed in lymphoid tissues. Because no related effects were observed in other endpoints, these changes were not considered to be adverse.

ADA were detected in animals during the dosing period only in the two lowest dose groups, eight in the 2 mg/kg group, and two in the 10 m/kg group.

A 6-month GLP pharmacokinetic/toxicity study has also been performed in the cynomolgus monkey. Animals of both sexes were dosed IV with XmAb5871 or vehicle control every other week for a total of 13 doses at 0, 10, 50, or 200 mg/kg. No mortalities occurred in the study and no test article-related effects were identified in clinical observations, body weight, electrocardiography and ophthalmology assessments, urinalysis, hematology, serum chemistry and coagulation parameters, and gross and microscopic anatomic evaluations. Test article-related effects were limited to dose-related reductions in B cells (CD3-CD20+) observed from Day 15 through Day 183. At all doses, the reduction observed after the first dose was maintained throughout the dosing period with no notable further reduction with subsequent doses. The B cell count was reduced to approximately 45-50%, 30-35% and 25-30% of baseline values in the 10 mg/kg, 50 mg/kg and 200 mg/kg groups. At all doses, evidence of recovery was observed by Day 281 (3 months after the last infusion) with levels recovering to within 80% of baseline levels by the end of the study (Day 358). These effects were considered not adverse as no related changes were observed in other endpoints.

In summary, no adverse test article-related effects have been seen in cynomolgus monkeys following IV infusions of up to 200 mg/kg XmAb5871 every 14 days for up to 6 months. These studies therefore identified a no observed adverse effect level (NOAEL) of 200 mg/kg, the highest dose studied. A detailed description of the non-clinical studies is presented in the XmAb5871 Investigator's Brochure.

1.3. Clinical Studies

A FIH, single ascending dose study with XmAb5871 (XmAb5871-01) in healthy volunteers and a multiple ascending dose study in RA patients (XmAb5871-02) have been completed.

1.3.1. A Randomised, Blinded, Placebo-Controlled, Single Ascending Dose Study of the Safety, Tolerability, and Pharmacokinetics of XmAb®5871 in Healthy Adult Volunteers

In the FIH study, 48 healthy male subjects were enrolled and were randomized 3:1 (XmAb5871:placebo) to receive a single IV infusion of XmAb5871 or matching placebo administered over a 2 hour period in a double-blinded manner. Thirty-six subjects received single IV infusions of XmAb5871 at 0.03 mg/kg (N=3), 0.1 mg/kg (N=3), 0.2 mg/kg (N=7), 0.6 mg/kg (N=6), 2.0 mg/kg (N=6), 5.0 mg/kg (N=6) and 10.0 mg/kg (N=5) dose levels. Twelve subjects received placebo. All completed the study.

XmAb5871 was moderately well tolerated at the doses investigated. No subjects experienced a serious adverse event (SAE) or dose limiting toxicity and no subjects discontinued the study prematurely. A total of 32/36 XmAb5871 subjects (88.9%) reported at least 1 treatment-emergent adverse event (TEAE). The percentage of subjects who experienced TEAEs in the active group was similar to that of the subjects in the placebo group (11/12 subjects [91.7%]). The most common TEAEs were gastrointestinal-related: nausea, vomiting, abdominal pain, abdominal discomfort, epigastric discomfort and diarrhea. Such gastrointestinal-related TEAEs were reported by 14/36 XmAb5871 subjects (38.9%), but no placebo subjects. Symptoms were assessed as mild or moderate in severity in all except one subject, a subject in the 10.0 mg/kg cohort, who reported nausea of severe intensity. Eight subjects (22%), at doses of 0.2 to 10.0 mg/kg, had their XmAb5871 IV infusion temporarily interrupted as a result of the infusion-related gastrointestinal symptoms; all subjects were able to continue the infusion after a short interruption and symptoms did not recur. No concomitant medication was required for relief of symptoms. There were no consistent trends in hematology, coagulation, clinical chemistry, immunoglobulin levels, electrocardiogram (ECG), or vital sign parameters reported.

Pharmacokinetic analysis indicated that serum concentrations of XmAb5871 increased in an approximately dose proportional manner and declined in an apparent mono-phasic manner.

Clearance decreased with increasing dose approaching a constant value at the higher dose levels. Volume of distribution decreased with dose increment approaching a value that was similar to physiologic serum volume. Half-life tended to increase with dose but was relatively constant at the four highest dose levels, averaging 3.63 +/- 1.24 days. Circulating B cell CD19 was completely saturated at all dose levels and there was a strong relationship between dose and time to CD19 desaturation.

Sixteen of 36 (44%) XmAb5871 treated subjects had at least one sample positive for ADA. There was no distinct evidence of ADA mediated clearance of XmAb5871 in any ADA positive subject other than one subject (5 mg/kg) in whom an accelerated decline in XmAb5871 concentration was observed in the terminal portion of the concentration time curve. All positive ADA samples were negative in a bioassay to detect neutralizing antibodies against XmAb5871.

A dose-related reduction of CD20+ B cell count followed XmAb5871 administration. The nadir mean CD20+ B cell counts of roughly 40% to 50% of baseline cell counts occurred between approximately Day 4 and Day 8. The degree of the CD20+ B cell count reduction at nadir did not significantly increase as dose of XmAb5871 increased. The recovery of the B cell count approximated the observed kinetics of XmAb5871 clearance. There was no association observed between the presence of the FcγRIIa R131 polymorphic allele and the CD20+ B cell count at nadir.

Expression of CD86 on B cells is induced by a signaling pathway event downstream of the BCR. At all doses evaluated, XmAb5871 suppressed the expression of CD86 in ex vivo stimulated B cells. This observation is consistent with the proposed mechanism of action of XmAb5871; namely, down-regulation of the BCR signaling pathway. XmAb5871 also attenuated the mean anti-tetanus toxoid (TT) response in subjects after a single administration at doses of ≥0.2 mg/kg. Additional information on the FIH study can be found in the Investigator Brochure.

1.3.2. A Randomized, Placebo-Controlled, Double-Blinded, Ascending Multiple-Dose Study of the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of XmAb®5871 in Patients with Rheumatoid Arthritis

A randomized, double-blinded, ascending multiple-dose Phase 2a study has also been completed using investigational sites in Hungary, Poland, Slovakia and the Czech Republic. This study enrolled RA patients who had active disease on stable non-biologic disease modifying anti-rheumatic drug (DMARD) therapy. The completed Phase 2a study was enrolled in two parts:

- Part A administered doses of XmAb5871 at 0.3, 1.0, 3.0 or 10.0 mg/kg or matching placebo (3:1 randomization) by a 2-hour infusion for up to 6 consecutive doses given at 2 week intervals.
- Part B was an extension cohort of 10.0 mg/kg or placebo (2:1 randomization) given up to 6 times at 2 week intervals.

A total of 57 RA patients (41 XmAb5871, 16 placebo) were enrolled in the study, 30 in Part A and 27 in Part B. One patient randomized to XmAb5871 discontinued the study before being dosed. Twenty-two patients received XmAb5871 in Part A. Three patients received 6 doses of 0.3 mg/kg XmAb5871, 6 patients at each dose level received 6 doses of 1.0, 3.0, and 10.0 mg/kg and one additional patient received 2 doses of 10.0 mg/kg before discontinuing the study.

In Part B, 15 patients received 6 doses of 10.0 mg/kg XmAb5871 and 3 patients received 1-3 doses each before discontinuing the study. Across the study, a total of 223 doses of active drug were administered, of which 2 were partial infusions that were not completed.

XmAb5871 was generally well tolerated at doses investigated. A total of 103 TEAEs were reported in 30/40 (75.0%) of the XmAb5871-treated patients. Of these, 49 of the 103 (47.6%) were regarded as unrelated or unlikely to be related to administration of XmAb5871. As seen in the FIH study, the most common treatment-related AEs in the XmAb5871 groups were nausea, vomiting and diarrhea that occurred during the first infusion in 10 of the 40 XmAb5871-treated patients (25%). The gastrointestinal symptoms were generally mild to moderate, with vomiting of severe intensity reported by only one patient (10.0 mg/kg XmAb5871). Nine patients (23%) had their first XmAb5871 IV infusion temporarily interrupted as a result of the infusion-related gastrointestinal symptoms (vomiting/nausea or diarrhea). Seven of the 9 (78%) occurred in the 10.0 mg/kg cohort. In all cases the patients were able to continue the infusion after a short interruption (5-31 minutes) and symptoms did not generally recur on continuation of the infusion or during subsequent infusions. There were no consistent trends in hematology, coagulation, clinical chemistry, immunoglobulin levels, electrocardiogram (ECG), or vital sign parameters reported.

A total of 2 XmAb5871 treatment-emergent SAEs in 2 patients were reported during the phase 2a study, both in the 10.0 mg/kg XmAb5871 group. One case of lower extremity deep venous thrombosis occurred during the follow-up period, 22 days after the last infusion. The SAE was considered to be possibly related to XmAb5871 by the investigator, but because the onset of the event occurred more than 6 half-lives after the last infusion, the Sponsor considered the event unlikely to be related to XmAb5871. The other SAE was a case of infusion-related reaction that

occurred at the time of the second infusion of XmAb5871 and was assessed to be definitely related to the administration of XmAb5871 by the investigator. A second patient also experienced an infusion-related reaction with hypotension (non-SAE) of moderate severity during the first infusion. Both were on the 10.0 mg/kg dose and were discontinued from the study. The nature and severity of these infusion-related reactions were consistent with those reported for other monoclonal antibody therapies.

Pharmacokinetic analysis indicated that serum concentrations of XmAb5871 decreased in an apparent mono-phasic manner over time. C_{max} for the first and last dose increased in a slightly greater than proportional manner with dose while the AUC for the first and last dose increased in a manner proportional with dose increment. At the dose levels studied, neither clearance nor volume of distribution showed any significant dose dependence, either for the first or last dose. There was little accumulation between the first and last doses with the every 14-day dosing interval.

Across all 4 dose levels, last dose clearance averaged 15.16 ± 3.68 mL/day/kg. Last dose volume of distribution averaged 49.27 ± 14.17 mL/kg. This figure is close to the literature value for physiological serum volume. Last dose half-life averaged 3.51 ± 1.06 days.

There was no statistically significant difference in clearance or volume of distribution between any of the receptor alleles for either FcγRIIa or FcγRIIb.

Complete CD19 receptor occupancy was seen at doses of 1.0, 3.0, and 10.0 mg/kg from first dose through the completion of dosing. Peripheral B cell count decreased in all cohorts following the first dose, with cohort mean levels of approximately 52-79% of baseline. The level of reduction did not increase with increasing dose or with subsequent doses and recovered to a mean cohort level of ≥ 80% of baseline levels during the post-treatment period.

Samples positive for anti-drug antibodies (ADA) were found in 7 of 40 (17.5%) XmAb5871-treated patients and in 1 of 16 (6.25%) placebo-treated patients. With the exception of the placebo-treated patient, all of the ADA were observed in the 10.0 mg/kg group. Only 2 of the 7 patients had positive ADA samples that remained positive after a >2-fold dilution (i.e., the majority were of low titer). One of these 2 patients experienced apparent hypersensitivity reactions with vomiting, fever and chills during the second infusion and vomiting, fever, and erythema during the third infusion. This was associated with the development of an ADA response with titers that increased over time. There was no distinct evidence of ADA mediated clearance of XmAb5871 in any ADA positive patient.

In Part B of the study, more patients treated with XmAb5871 (10.0 mg/kg) achieved DAS28-CRP low disease or remission at Day 85 than did the placebo treated patients (5/15 vs 0/8; 33% vs 0%). In addition, 40% (6/15) of the XmAb5871 treated patients achieved an ACR50 and 20% (3/15) achieved an ACR70. By comparison, 12.5% (1/8) and 0% (0/8) of the placebo-treated patients achieved ACR50 and ACR70 responses, respectively.

The Sponsor will immediately notify the Principal Investigators if any additional safety or toxicology information becomes available during the study. A detailed description of the completed clinical studies is presented in the XmAb5871 Investigator's Brochure.

1.4. Rationale for the Clinical Study

Although glucocorticoids are effective in SLE, long term use of these agents is not optimal and disease exacerbations are common as the therapy is tapered. There is a clear need for ongoing development of new drugs with different modes of action, different pathways, improved safety profiles and quality of life benefits. Therapy to reduce B cell proliferation by depleting a needed growth factor, BAFF or BLyS, (belimumab) has been licensed as a therapy for SLE and it stands to reason that other therapies directed at B cell function by a different mechanism of action may also be shown to be efficacious, potentially even in non-overlapping subsets of patients.

FcγRIIb has been shown to play a crucial role in suppressing autoimmunity. For example, autoimmune disease is exacerbated in mice lacking FcγRIIb (Nimmerjahn et al, 2008), and its restoration rescues mice in SLE, arthritis, and asthma models (Brownlie et al 2008, Dharajiya et al 2010, McGaha et al 2005). Moreover, FcγRIIb polymorphisms affecting activity or expression are associated with human autoimmunity (Floto et al 2005, Tsuchiya et al 2006, Tarasenko et al 2007) and B cell expression of FcγRIIb is dysregulated in SLE (Mackay et al 2006). Despite the dysregulation of FcγRIIb in SLE, XmAb5871 was able to inhibit human SLE B cells in vitro (Horton et al 2011). The presumed role of B cells and plasmablasts in SLE and the observations of beneficial effects on SLE disease activity by B cell directed therapies support the evaluation of non-depleting B cell directed therapies such as XmAb5871 in patients with SLE. The proposed dose and dosing regimen is based on available data from the non-clinical pharmacology and toxicology studies and available data from the completed human studies.

The GLP 6-month, repeat-dose toxicity study in cynomolgus monkeys consisted of 13 infusions administered every other week, a dosing schedule and duration matching that of the proposed pilot study of XmAb5871 in human patients with SLE. The maximum dose administered and the NOAEL in the cynomolgus monkey study was 200 mg/kg. XmAb5871 was generally well-tolerated when given at doses up to 10.0 mg/kg every other week for 6 doses in patients with RA

(see above), and there was no evidence of any cumulative toxicity over the 6 doses. Complete CD19 receptor occupancy was observed in the repeat dose RA study at doses of 1.0, 3.0, and 10.0 mg/kg from first dose through the completion of dosing. Trends in improvement in RA clinical disease activity were seen at all doses, particularly at 3.0 and 10.0 mg/kg. Based on the observed safety and tolerability profile, the effects on CD19 receptor occupancy and effects on disease activity in the RA trial, a dose of 5 mg/kg has been selected for this study.

1.4.1. Risk-Benefit Assessment

The risks and benefits for the use of XmAb5871 are currently assessed by the available non-clinical data and the information from the completed human studies. The preclinical data to date indicate that XmAb5871 was well tolerated in the cynomolgus monkey, the most relevant single toxicology species. Both 12-week and 6-month repeat dose GLP toxicity evaluations have been performed in cynomolgus monkey. No deaths occurred and no test article-related effects were identified in clinical observations, body weight, electrocardiography and ophthalmology assessments, urinalysis, hematology, serum chemistry and coagulation parameters, or in anatomic evaluations (gross and microscopic). At doses up to 200 mg/kg in the 6-month study, mean absolute and relative counts of B lymphocytes were observed to be decreased, relative to baseline levels, in a dose-related manner. B cell counts demonstrated recovery at day 281, and this recovery was sustained at day 358.

The differences between the binding affinities for XmAb5871 to human and cynomolgus monkey FcγRs should be considered in light of the toxicology results. The affinity of XmAb5871 for cynomolgus monkey FcγRIIb is approximately 250-fold less than that for human FcγRIIb. Although the desired pharmacologic effect was observed in cynomolgus monkey (i.e., down-regulation of BCR mediated B cell signaling), target-mediated toxicity may be more difficult to observe in the cynomolgus monkey than in humans. No significant toxicities have been observed in either of the two completed human studies, suggesting that the toxicology species is informative.

The observed reduction in absolute B cell count in both the human studies may have occurred from the result of redistribution of B cells from the circulation to central compartments, from direct anti-proliferative effect of CD19 engagement or from the inhibition of the B cell pro-survival effects induced by BCR signaling. These possibilities are not mutually exclusive. B cell counts can be monitored readily in clinical laboratories and the safety impact of even a substantial B cell reduction is considered minimal given the degree to which complete B cell depletion with rituximab is tolerated. The toxicity and pharmacologic action of B cell depletion is now understood well from years of clinical experience with primary B cell depleting agents

such as rituximab. Both the toxicology and human studies of XmAb5871 have indicated the reductions in B cell concentration are reversible following discontinuation of the study drug.

Both clinical studies completed to date have been randomized, double-blinded, placebo controlled studies with a primary endpoint of safety and tolerability. Therefore, the clinical benefit of XmAb5871 has not been established. The Phase 2a trial in RA was not powered for efficacy, but trends in improvement in RA disease activity among the XmAb5871-treated patients compared to those treated with placebo were observed.

1.4.2. Potential Risks

Based on preclinical toxicology studies, experience in human studies to date and class effects of immunomodulating monoclonal antibodies, patients receiving XmAb5871 may be at risk for the following adverse events:

1.4.2.1. Infusion-Related Reactions

All monoclonal antibody therapeutics are associated with the risk of both allergic (hypersensitivity) and non-allergic (cytokine release syndrome) infusion-related reactions. Most infusion-related reactions are mild and may be alleviated by interruption of the infusion and reinitiating the infusion at a slower infusion rate after symptoms abate.

No signs or symptoms of infusion-related reaction were observed in the FIH study. In the multiple dose Phase 2a study, two patients, both of whom had received XmAb5871 at 10.0 mg/kg, experienced infusion-related reactions with hypotension and were discontinued from the study. The first patient experienced a severe infusion-related reaction on the second infusion; the second patient's infusion-related reaction was considered moderate and occurred during the first infusion. In both cases, the infusion was stopped and symptomatic therapy given. The symptoms responded quickly and there were no sequelae. The nature and severity of the infusion reactions were consistent with those reported for other monoclonal antibody therapies. In addition, a third patient developed signs and symptoms of a hypersensitivity reaction during the second and third infusions, associated with the development of ADA prior to the second infusion with increasing titers thereafter. This patient was also discontinued from the study and also recovered without sequelae.

Although observed rarely, severe infusion-related reactions, including deaths following the administration of otherwise well-tolerated monoclonal antibodies, have been reported. Patients should be closely monitored during and after all infusions, as specified in the study protocol. In the case of an infusion reaction, the infusion should be stopped immediately and the patient managed as per the treatment guidelines listed in Section 6.1.2.3.6.

All investigators should be well trained in the management of acute infusion-related events including administration of epinephrine and other therapeutic modalities. Emergency resuscitation equipment and medications should be present for immediate use in the area where patients are receiving their infusions.

Patients should be monitored closely during and after infusion. XmAb5871 should be administered intravenously at a constant rate over a 2 hour period for the first infusion and over a 1-2 hour period for subsequent infusions. Patients will be continuously assessed during the infusion and for at least 1 hour following the end of infusion (2 hours following the first infusion). During the first infusion, vital signs including blood pressure, heart rate, respiratory rate and temperature assessments will be performed within 2 hours before the infusion, at 15, 30, 60 and 120 minutes after the start of infusion, and at the end of infusion (if different than 120 minutes from start of infusion). In addition, vital signs will be performed 15, 30, 60 and 120 minutes after the end of the first infusion.

The frequency of vital sign monitoring will be modified at subsequent infusions if the first infusion is tolerated well. At all subsequent infusions, vital signs will be assessed within 2 hours before the infusion, at 30 and 60 minutes after the start of infusion, at the end of infusion (if different than 60 minutes from start of infusion), and at 30 and 60 minutes after end of the infusion.

1.4.2.2. Infusion-Associated Gastrointestinal-Related Toxicity

The most common XmAb5871 AEs reported in both clinical studies have been the occurrence of nausea, vomiting, or diarrhea during the first XmAb5871 infusion. In the FIH study, 8 subjects (over the dose range 0.2 mg/kg to 10.0 mg/kg) had their XmAb5871 IV infusion interrupted temporarily as a result of the self-limiting gastrointestinal-related symptoms of short duration (abdominal discomfort, abdominal pain, epigastric discomfort, nausea and vomiting). In all cases, the subjects were able to continue the infusion after a short interruption (maximum total infusion duration was 2 hours and 54 minutes) and symptoms did not recur. No concomitant medication was required for alleviation of symptoms.

In the Phase 2a study, 9 patients (23%) had their first XmAb5871 IV infusion temporarily interrupted as a result of the gastrointestinal-related symptoms (nausea, vomiting or diarrhea). Seven of the 9 (78%) occurred in the 10.0 mg/kg cohorts. In all cases, the patients were able to continue the infusion after a short interruption (5-31 minutes) and symptoms did not generally recur on continuation of the infusion or during subsequent infusions. No concomitant medication was required for alleviation of symptoms.

The etiology of these symptoms is not clear. There are no known associations of CD19 or FcγRIIb and the gastrointestinal tract. Mild to moderate nausea, vomiting or diarrhea may occur during the first infusion of XmAb5871 and should be treated by interrupting the infusion for 15-30 minutes. The infusion may be restarted at the original rate once symptoms have resolved. Medication for symptomatic relief may be administered if required.

1.4.2.3. B-Cell Lymphopenia

B cell lymphopenia, with no notable effect on the total lymphocyte count, was observed in both nonclinical toxicology and clinical studies. In cynomolgus monkey, reductions in B cell levels were observed in the 2 repeat-dose GLP toxicology studies performed to date. In both the 12-week (6 infusions at doses up to 50 mg/kg) and 6-month (13 infusions at doses up to 200 mg/kg) toxicology studies in which XmAb5871 was administered IV every 2 weeks, reductions in cohort mean B cell count were observed. In the 12-week study, the B cell count was reduced to approximately 45-50%, 30-35% and 25-30% of baseline values in the 10 mg/kg, 50 mg/kg and 200 mg/kg groups. At all doses, evidence of recovery was observed by Day 281 (3 months after the last infusion).

As was the case in nonclinical toxicology studies, in both clinical studies performed to date, reductions in absolute B cell counts were observed with mean reductions to 50-60% of baseline levels and a maximum individual subject reduction to 22% of baseline. In both studies, the reductions in ABC were not associated with the presence of the FcγRIIa R131 genotype and were not associated with clinical adverse events.

The recovery of B cell counts after a single dose or multiple doses of XmAb5871 approximated the kinetics of the clearance of XmAb5871 from serum in the clinical studies. Although prolonged reductions in B cell counts to the extent seen with B cell depleting therapies have not been observed and are not expected following administration of XmAb5871, B cell depleting therapies have been widely used both in hematologic malignancies and in autoimmune disease states. Toxicity and pharmacologic action of B cell depletion is well understood and is a manageable risk in humans. Patients will be monitored with quantitation of B cell counts during the trial.

1.4.2.4. Infections

XmAb5871 is an immunomodulating agent by virtue of its effect on down regulation of B cell function. No severe or opportunistic infections have been observed in cynomolgus monkey toxicology studies or in the XmAb5871 clinical program to date, however all patients receiving any immunomodulating agent should be monitored for the development of infections, including those caused by bacterial, viral and fungal pathogens.

1.4.3. Potential Benefits

The primary purpose of the study is to evaluate the ability of XmAb5871 to maintain improvement in SLE patients following a brief course of disease-suppressing IM steroid therapy. Based on the effect of XmAb5871 on B cell function observed in *in vitro* and *in vivo* studies and on the trends in improvement in RA disease activity observed, some XmAb5871 treated patients may maintain the improvement in SLE disease activity induced by the brief course of IM steroid therapy for the 6-month duration of the study and not need to have additional therapeutics added for disease exacerbation. The study will use the SELENA SLEDAI (hybrid version) with the SELENA SLEDAI Flare Index, BILAG (2004 version) and Physician's Global Assessment of disease activity to evaluate the effect of XmAb5871 on disease activity over time.

1.4.4. Conclusion

XmAb5871 is being developed for the treatment of SLE, and a double-blind, randomized pilot efficacy trial is currently proposed. Given the established role of B cells in the pathogenesis of SLE, the effects of XmAb5871 on B cell function in the absence of complete B cell depletion may provide an attractive therapeutic option for this condition.

The trial design contains adequate measures to mitigate risk factors, and frequent safety monitoring is an inherent part of the protocol. In summary, the benefits and risk assessment for the application of XmAb5871 appears favorable and supportive for initiation of the proposed clinical trial.

This study will be performed in compliance with the protocol, International Conference on Harmonization (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements. Aspects of the study concerned with the investigational medicinal product(s) (IMPs) will meet the requirements of standard Good Manufacturing Practice (GMP).

2. STUDY OBJECTIVES

2.1. Primary Objective

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

2.2. Secondary Objective

- 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 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 over time

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This is a double blind, randomized multiple dose pilot study to investigate the efficacy, safety, tolerability, PK, immunogenicity and PD of XmAb5871 in patients with SLE. The study will be conducted in centers with expertise in evaluating patients with this disease.

All patients will receive 5.0 mg/kg of XmAb5871 or matched placebo over 1-2 hours IV on an every other week dosing schedule for a total of up to 16 doses. Patients will be followed for 6 weeks after the final infusion. Approximately 90 patients will be enrolled with a 1:1 randomization of XmAb5871: placebo.

Patients will enter screening with 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 receive a brief course of IM steroid therapy. After obtaining informed consent, appropriate screening studies will be performed and 160 mg of IM depomedrol will be administered. Over the next 2-4 weeks of the screening period, per PI discretion, patients may receive additional IM depomedrol injections (up to an additional 320 mg during screening) to treat their SLE symptoms to a target of disease 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. Patients on anti-malarial therapy may continue on their usual dose. Patients on oral doses of ≤15 mg of Prednisone per day (or the equivalent) will be tapered to

10 mg or less per day by randomization (Day 1) and then may continue on this dose throughout the study. Patients who do not meet the disease activity improvement criteria by Day 1 will not be randomized into the study and their participation will end.

Patients must have documented SLE disease activity improvement following the brief course of IM steroid therapy 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 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 primary and secondary efficacy endpoints. On Day 1, baseline procedures such as physical exam, blood and urine samples for laboratory assessments, PK and PD samples will be collected and 80 mg of IM depomedrol will be given prior to administration of study drug. The first infusion of either XmAb5871 or placebo will be given IV over a period of 2 hours. Patients will be observed for at least 2 hours after the 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 Day 15, patients will receive an additional 80 mg of IM depomedrol to sustain the disease activity improvement long enough for XmAb5871 to reach a steady state level. On Day 15 and on study Days 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, 169, 183, 197, and 211 patients will return for XmAb5871 (5 mg/kg) 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 loss of disease improvement (LOI) as defined by:

I. The assessment by the principal investigator that the 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: 1) a SELENA SLEDAI increase of ≥4 points from maximal improvement; OR 2) a worsening of at least one BILAG A or B score; OR 3) the appearance of a new A or B.

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, i.e., will be

discontinued from the study, and **may receive any appropriate SLE therapy at the discretion of the principal investigator.**

Patients who discontinue the study early either because of loss of improvement or for other reasons will be followed for safety for a further period of 6 weeks after their last dose of XmAb5871 or placebo (completing assessments in schedule of events listed as Day 225 as the LOI visit and Day 253[EOS] visit 4 weeks later) at which time their participation is completed.

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 or clinically significant safety lab abnormalities will be followed until resolution or until the TEAEs/abnormalities are stabilized.

The effect of XmAb5871 on maintenance of improvement of SLE disease activity will be evaluated as the percentage of patients without loss of improvement at Day 225 (primary endpoint) and Day 169 (secondary endpoint).

Assessments will include AE assessment, physical examination, vital signs, ECG, clinical laboratory tests (hematology, clinical chemistry, B cell and T cell levels, immunoglobulin levels, urinalysis, coagulation, PK, PD and immunogenicity.

Pharmacodynamics of XmAb5871 will be evaluated by serial measurements of CD19 receptor occupancy (RO) and by enumeration of circulating B cells and their subsets.

FcγR polymorphisms will be assessed by FcγRIIa and FcγRIIb genotyping.

Please refer to Table 6 Schedule of Assessments for a detailed list of procedures performed on each study day/visit.

3.2. Discussion of Study Design

In the previously completed Biomarkers of Lupus Disease (BOLD) study of SLE patients in whom a brief course of IM steroid therapy induced SLE disease activity improvement following the cessation of background immunosuppressant therapy, 40/41 patients lost the disease activity improvement by month 6, equivalent to a 2.4% placebo response. Assuming a 10% placebo response rate will be observed in this study and assuming that XmAb5871 will provide a 38% response rate (preventing loss of disease activity improvement), the number of patients needed for 80% power and 5% significance would be 40 per arm. Adding approximately 10% for

drop-outs, the total number per arm is calculated as 45. The study is designed to obtain information on the ability of XmAb5871 to maintain improvement of SLE disease activity after a brief course of IM steroid therapy. Safety of XmAb5871 in SLE will also be evaluated.

The protocol has been amended to change the time of the primary endpoint from 6 months to 8 months to account for the more prolonged initial course of IM steroid therapy being given in this study relative to the BOLD study.

3.3. Selection of Patient Population

It is anticipated that approximately 90 SLE patients will be enrolled in the study. Patients appropriate for screening will have active SLE without organ-threatening involvement, will be able and willing to discontinue their background ineffective immunosuppressive medications, and will be willing to receive a brief course of IM steroid therapy. Those that achieve a protocol defined level of disease activity improvement will be randomized to receive XmAb5871 or placebo and will be followed for the loss of the disease activity improvement effected by the IM steroid therapy.

3.4. Endpoints

The study involves assessments of SLE disease activity, safety, immunogenicity, PK, PD and pharmacogenomics. The specific endpoints are listed below.

3.4.1. Disease Activity

The primary endpoint will be evaluated as the percentage of patients without loss of disease activity improvement at Day 253. The percentage of patients without loss of disease activity improvement on Day 169 and time to loss of disease activity improvement will be evaluated as secondary endpoints. In addition, the following disease assessment indices may be used for exploratory analyses of SLE disease activity over time:

- SELENA SLEDAI hybrid version with SELENA SLEDAI Flare index
- BILAG 2004
- Physician's Global Disease activity VAS

3.4.2. Mechanistic Studies

Blood will be collected and analyzed at Screening, Day 1, Day 29 and either at the first visit with loss of disease activity improvement (LOI) or 2 weeks after the last infusion (Day 225), whichever comes first. The following biomarkers will be explored: changes in autoantibody profiling by BioPlex 2200, multiplex evaluation of plasma cytokines, RNA expression to

determine changes in selected BCR, BAFF and IL4-mediated signaling responses, and a broader, more exploratory evaluation of cytokine and gene expression evaluated via hierarchical clustering and principal component analyses. Samples will be collected and stored from additional visit days as given in Table 6 to be utilized for future evaluation of additional analytes as deemed appropriate from initial studies. The results from these studies may be reported separately from the clinical study report.

3.4.3. Safety Endpoints

- Physical examinations
- Vital signs (supine blood pressure [BP], heart rate, oral body temperature, respiratory rate [RR]) (during the infusion of XmAb5871, vital signs will be obtained in the semi-supine sitting position)
- Adverse event assessments
- Twelve-lead electrocardiograms (ECG): PR interval, QRS interval, RR interval, QT interval, and QTc interval (Bazett's correction [QTcB] and Fridericia's correction [QTcF])
- Clinical laboratory testing (hematology, coagulation, clinical chemistry, and urinalysis)
- B cell and T cell quantification by flow cytometry
- Concomitant medication assessments
- Serum immunoglobulin (Ig) levels (IgG, IgM, IgE)
- Complement levels C3 and C4
- Monitoring for pregnancy in women of child-bearing potential only

3.4.4. Immunogenicity Endpoint

- Frequency and titer of anti-XmAb5871 antibodies (anti-drug antibodies [ADA])

3.4.5. Pharmacokinetic Endpoints

Predose (trough) and end-of-infusion (peak) XmAb5871 serum concentrations will be measured on selected infusions, at the endpoint disease assessment timepoint and at EOS. No PK parameters will be computed because no extensive serial post-dose sampling will be done in this study.

3.4.6. Pharmacodynamic Endpoints

- Absolute B cell counts (ABC)
- Autoantibody and cytokine levels

3.4.7. Pharmacogenomics Endpoints

- FcγRIIa R131H polymorphism
- FcγRIIb I232T polymorphism

3.5. Stopping Criteria for the Clinical Study

Participation for any individual patient will be stopped if the patient experiences a possibly drug-related serious adverse event (SAE) or a possibly drug-related significant non serious AE, which in the opinion of the PI or Sponsor's medical representative, warrants discontinuation of the study for that patient's well-being. Discontinuation of the patient from the study will be discussed with the Sponsor.

The Investigator will make all appropriate safety assessments on an ongoing basis. The Sponsor's medical representative will review individual safety information as it becomes available throughout the study. In addition, unblinded aggregate safety information will be reviewed by an external Safety Review Committee (SRC) after approximately 15 patients have completed the study, and after approximately 45 and 75 patients have completed the study. The SRC will consist of, at a minimum, two rheumatologists with SLE expertise and a biostatistician who will review the data in an unblinded manner. The coordinating investigator and the medical representatives of the Sponsor (Xencor) and the CRO (PPD) will review blinded data only. 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.

3.6. Dose Delay and Dose Modification in Patients Who Experience Toxicity

Patients experiencing a ≥Grade 2 drug-related hematologic or non-hematologic toxicity will have subsequent dosing held until recovery to baseline or ≤Grade 1 values following the AE. Patients who enter the study with pre-existing disease-related abnormalities of >Grade 1 will have subsequent dosing held if there is drug-related worsening to Grade 3. Dose will be held until recovery to baseline or ≤Grade 1 values following the worsening.

In the event that drug-related toxicity persists for >21 days or such that two consecutive doses are missed, the patient will be permanently discontinued from the study drug treatment.

There will be no dose level modification in this study.

4. STUDY POPULATION

Patients eligible for screening are men and women ages 18 to 65 inclusive with active SLE, defined as a SELENA SLEDAI of ≥6 (≥4 points of which must come from non-serological findings) OR at least one BILAG A or B score. If a single BILAG B score is based on arthritis, there must be at least 3 tender and at least 3 swollen joints out of 28 joints counted. If a single BILAG B score is based on rash, there must be involvement of at least 9% of body surface area for at least one week, or 5% of body surface area for discoid skin rash. Patients must be able to provide written informed consent and meet all the inclusion criteria and none of the exclusion criteria. They must be able and willing to stop their immunosuppressants and to be given a brief course of IM steroid therapy. In the judgment of the investigator, they must have non-organ threatening disease (e.g. there is no active nephritis requiring either ongoing induction or maintenance therapy, or any other solid organ, CNS or hematologic disorder for which stopping SLE therapy is contraindicated). Only patients who have protocol defined disease activity improvement by Day 1 will be randomized.

4.1. Number of Patients

It is anticipated that approximately 90 patients will be enrolled in the study. In a previously completed study of SLE patients in whom a brief course of IM steroid therapy induced SLE disease activity improvement following the cessation of background immunosuppressant therapy, 40/41 patients lost the disease activity improvement by month 6; equivalent to a 2.4% placebo response. If we assume that XmAb5871 will provide a 38% response in preventing loss of disease activity improvement, the number of patients needed for 80% power and 5% significance would be about 40 per arm. Adding 10% for unevaluable patients, the total number per arm is calculated as 45.

4.2. Inclusion Criteria

Patients who meet the following criteria will be considered eligible to participate in the clinical study:

1. Able to provide written informed consent.
2. Adult males and females aged 18 to 65 years inclusive with a diagnosis of SLE as defined by the ACR Criteria (≥4 criteria fulfilled).
3. Patients have a history of a (+) ANA, (+) ENA (anti-RNP or anti-Smith) or a (+) anti-dsDNA serology documented by laboratory report within the year prior to randomization.

4. The Principal Investigator has assessed the patient and in their judgment, the disease activity is not organ threatening (e.g. there is no active nephritis requiring either ongoing induction or maintenance therapy, or any other solid organ, CNS or hematologic disorder for which stopping SLE therapy is contraindicated).
5. Both investigator and patient agree that it is acceptable to discontinue their current immunosuppressant SLE medications and receive a brief course of IM steroid therapy.
6. Patients must have active disease at screening defined as:
    a. A SELENA SLEDAI of ≥6 (≥4 points of which must come from non-serological findings)
    b. OR ≥1 BILAG B score
        i. If a single BILAG B score is based on arthritis, there must be at least 3 tender and at least 3 swollen joints out of 28.
        ii. If a single BILAG B score is based on rash, there must be involvement of at least 9% of body area for at least one week, or 5% of body area for discoid skin rash.
    c. OR ≥1 BILAG A score
7. To be eligible for randomization on Day 1, patients must have documented disease improvement defined as:
    a. SELENA SLEDAI decrease of ≥4 points OR
    b. Decrease in BILAG of ≥1 severity grade in at least one organ system that began with A or B (clinical criteria without temporal criteria) by Day 1.
8. If patients are on oral steroids, they must be on the equivalent of ≤15 mg/day of prednisone to enter screening AND must be able to taper to ≤10 mg/day by randomization.
9. Subjects must have the following laboratory parameters at screening:
    a. White blood cell count $\geq 1.5 \times 10^3/\mu L$.
    b. Absolute neutrophil count (ANC) $\geq 1.0 \times 10^3/\mu L$.
    c. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) at screening ≤2.5 × upper limit of normal (ULN).
    d. Serum creatinine ≤2.5 mg/dL.

e. Hemoglobin ≥8 g/dL.

f. Platelet count ≥40,000 × 10^9/L.

10. Subject must be able to comply with the dosing instructions for study drug administration and able to complete the study schedule of assessments.

4.3. Exclusion Criteria

Patients who meet one or more of the following criteria will not be considered eligible to participate in the clinical study:

1. History or evidence of a clinically unstable/uncontrolled disorder, condition or disease (including but not limited to cardiopulmonary, oncologic, renal, metabolic, hematologic or psychiatric) other than SLE that, in the opinion of the Principal Investigator would pose a risk to patient safety or interfere with the study evaluation, procedures or completion.
2. Patients who have organ threatening manifestations of SLE including active Class 3 or 4 lupus nephritis requiring induction or maintenance therapy or any other disorder for which stopping SLE therapy is contraindicated.
3. Active CNS lupus such as seizures or psychosis that in the opinion of the investigator would preclude participation.
4. Unstable hemolytic anemia or thrombocytopenia.
5. Malignancy within 5 years (except successfully treated in situ cervical cancer or squamous or basal cell carcinoma of the skin).
6. Active infection requiring hospitalization or treatment with parenteral antimicrobials within the 60 days prior to randomization, oral antimicrobials within 21 days prior to randomization.
7. Patients who have received live vaccines within 2 months of randomization.
8. Positive test for hepatitis B surface antigen, hepatitis B core antibody or hepatitis C antibody.
9. Positive urine pregnancy test (i.e., urine human chorionic gonadotropin [hCG]) at screening, on Day 1, or any other time during the study.
10. Patients who do not agree to use medically acceptable methods of contraception (as defined in Section 5.10.2).

11. Patient is pregnant or breast feeding, or planning to become pregnant while enrolled in the study, up to End of Study (EOS) visit.
12. Male patient with a pregnant partner who is not willing to use a condom during the treatment and up to EOS visit.
13. In the judgment of the investigator any clinically-relevant drug or alcohol abuse within 12 months of screening that may interfere with subject treatment, assessment or compliance with the protocol.
14. Use of any investigational agent within 5 half-lives of the agent (or 6 months if the half-life is unknown) prior to randomization.
15. Use of any biologic therapy (including belimumab) within 6 months of randomization or prior exposure to a monoclonal antibody directed to CD20 (such as rituximab) within 12 months of randomization.
16. Patients with a known or suspected sensitivity to products from mammalian cell lines.
17. Patients who cannot communicate reliably with the Investigator.
18. Patients who are unlikely to co-operate with the requirements of the study in the opinion of the Investigator.

4.4. Patient Withdrawal and Replacement

Patients are encouraged to complete all study evaluations; however, they may withdraw from the study at any time and for any reason. Every effort will be made to determine why any patient withdraws from the study prematurely. At the time that a patient withdrawals prematurely for any reason, all assessments as listed for the Day 225 visit should be performed. In addition, the patient should be scheduled for a follow-up visit 6 weeks from the time of the last infusion of study drug, at which time all assessments as listed for the Day 253 (EOS) visit should be performed. All patients who withdraw from the study with an ongoing AE must be followed, if at all possible, until the event is resolved or deemed stable by the investigator.

Patient participation may be terminated prior to completing the study and the reason recorded as follows:

1. Adverse event
2. Protocol violation
3. Loss to Follow-up
4. Patient withdrew consent

5. Other

A comprehensive effort must be made to determine the reason(s) why a patient fails to return for the necessary visits or is discontinued from the study. If the patient is unreachable by telephone, a registered letter, at the minimum, should be sent to the patient requesting him/her to contact the study site.

Patients withdrawn due to AEs considered to have a possible relationship to study drug will not be replaced. Patients withdrawn for a non-drug related reason will be replaced where the Sponsor deems necessary. The decision regarding the replacement of patients will be documented.

4.5. Termination of the Clinical Study

If the Investigator or the Sponsor becomes aware of conditions or events that suggest a possible hazard to patients if the clinical study continues, then the clinical study may be terminated after appropriate consultation among the involved parties. The clinical study may be terminated at the Sponsor's discretion also in the absence of such a finding.

Conditions that may warrant termination of the clinical study include, but are not limited to:

- The discovery of an unexpected, relevant, or unacceptable risk to the patients enrolled in the clinical study;
- Failure to enroll patients at the required rate;
- A decision of the Sponsor to suspend or discontinue development of the IMP.

Should the study be terminated and/or a site be closed for any reason, all documentation pertaining to the study and IMP must be returned to the Sponsor. Any actions required for assessing or maintaining study patient safety will continue as required, despite termination of the study by the Sponsor.

5. INVESTIGATIONAL MEDICINAL PRODUCT

5.1. Identity of the Investigational Medicinal Products

XmAb5871, the IMP, is an Fc engineered humanized mAb that binds to human CD19. XmAb5871 contains a modified IgG1 heavy chain Fc region that contains two amino acid substitutions in the Fc portion of the heavy chain that results in an increase in affinity to FcγRIIb binding relative to the native IgG1 Fc.

XmAb5871 drug product will be manufactured by Catalent, Madison, Wisconsin. The facility has been configured for GMP manufacture of biological products.

XmAb5871 drug product will be a sterile liquid product supplied in single-use glass vials. Each 10 mL glass vial is filled with 10.5 mL of drug product that contains 10 (+/-5%) mg/mL of XmAb5871, 10 mM sodium phosphate, 150 mM sodium chloride and 0.01% (w/v) polysorbate 20 at pH 7.2.

Active substance: XmAb5871

Activity: Humanized anti-CD19, Fc (fragment, crystallizable) engineered mAb with enhanced binding to FcγRIIb

Tested indication: SLE

Strength: 10 (+/-5%) mg/mL

Dosage form: Solution for infusion

Route of administration: IV infusion

Matching placebo without active substance will be supplied also as a solution for IV infusion.

5.2. Drug Storage and Handling Requirements

All study medication should be maintained in a storage area of the Pharmacy in a secure, temperature controlled, locked environment with restricted access. XmAb5871 or placebo must be stored under refrigeration at 2 to 8^{o}C (+/- 5^{o}C). Prior to administration, the parenteral drug product should be removed from storage temperature conditions and allowed to equilibrate to room temperature. Undiluted XmAb5871 or placebo is stable for up to 24 hours at room temperature; however Xencor must be notified if the drug product is left at room temperature for more than 8 hours. XmAb5871 or placebo should be mixed by swirling the vial gently before diluting to the dosing solution. **DO NOT SHAKE**; excess agitation may cause aggregate formation and foaming.

The full calculated dose will be administered based on the patient's Day 1 weight. The administered dose will be adjusted on subsequent infusion days **ONLY** if the weight on the infusion day differs more than 10% from the weight on Day 1. The XmAb5871 dose for patients whose weight exceeds 100 kg will be calculated based on a weight of 100 kg.

XmAb5871 or placebo will be diluted to a final concentration of 5.0 mg/mL in an infusion bag containing 0.9% sodium chloride for injection, USP. Prior to dilution, the parenteral drug

product should be inspected visually. The drug product should appear clear to slightly opalescent, colorless to yellow; practically free of particulates. If particulate matter and/or discoloration are noted, the drug should **NOT** be administered. XmAb5871 or placebo should not be mixed or diluted with other drugs or diluents such as 5% dextrose in water (D5W).

The bag should be gently inverted 2 or 3 times to mix the solution. The bag must not be shaken; excess agitation may cause aggregate formation.

Administration of XmAb5871 or placebo will be performed as described in the Pharmacy Manual, which will be provided to the sites.

Diluted XmAb5871 or placebo should be administered IV at a constant rate over a 1-2 hour period. XmAb5871 SHOULD NOT BE ADMINISTERED AS AN INTRAVENOUS PUSH OR BOLUS.

Vials are single-use containers. All unused supplies of XmAb5871 and placebo will either be destroyed or returned to the study Sponsor at the end of the study in accordance with instruction by the Sponsor.

5.3. Drug Administration

Administration of XmAb5871 or placebo should take place as soon as possible following dilution. If a delay is anticipated, diluted XmAb5871 or placebo may be stored at 2 to 8^{o}C for no more than 24 hours or at room temperature for no more than 8 hours prior to infusion. Diluted parenteral drug product should be administered intravenously at a constant rate over a 2 hour period for the first infusion and over a 1-2 hour period for subsequent infusions. XmAb5871 **SHOULD NOT BE ADMINISTERED AS AN INTRAVENOUS PUSH OR BOLUS**.

5.4. Dose Rationale

The proposed dose and dosing regimen is based on available data from the non-clinical pharmacology and toxicology studies with XmAb5871 and available data from the completed human studies.

The maximum dose administered and the NOAEL in the GLP 6-month, repeat-dose toxicity study in cynomolgus monkey (IV infusion every other week × 13 infusions) was 200 mg/kg. The dosing schedule and duration of the toxicity study provides support for the dose/schedule of the proposed study. The completed FIH study examined single doses from 0.03 mg/kg, a dose predicted to result in a C_{max} about 5-fold below the estimated minimum anticipated biological effect level to 10.0 mg/kg, a maximum dose based on predicted human PK and PD profiles, adequate safety margins, and practical considerations. These doses were generally well tolerated

in the single ascending dose study as well as in the 3-month multiple ascending dose study (QOW dosing × 6 doses) in RA patients. Complete CD19 receptor occupancy was seen in the repeat dose RA study at doses of 1.0, 3.0, and 10.0 mg/kg from first dose through the completion of dosing. A trend towards beneficial effects on RA disease activity could be seen in both the 3.0 and 10.0 mg/kg cohorts as well as in the comparison of XmAb5871 treated (all doses) vs all placebo treated patients.

Based on the observed safety and tolerability profile, the effects on CD19 receptor occupancy, and effects on disease activity in the RA study, a dose of 5 mg/kg has been selected for this study.

5.5. Supply, Packaging, and Labeling

XmAb5871 and placebo will be supplied by Almac. Investigational medicinal products will be packaged and labeled according to applicable local and regulatory requirements.

XmAb5871 will be a liquid product supplied in single-use glass vials. Each 10 mL glass vial is filled with 10.5 mL of drug product that contains 10 (+/-5%) mg/mL of XmAb5871, 10 mM sodium phosphate, 150 mM sodium chloride and 0.01% (w/v) polysorbate 20 at pH 7.2. Each product vial is intended to deliver at least 10 mL of drug solution or 100 mg (+/- 5%) of XmAb5871. Matching placebo without active substance will also be supplied as a solution for infusion.

All supplies of IMPs must be stored in accordance with the manufacturer's instructions. The IMPs will be stored in a secured area, accessible to authorized persons only, until needed for dosing.

5.6. Drug Accountability, Dispensing and Destruction

The Investigator or designee is responsible for maintaining accurate accountability records of the IMPs throughout the clinical study. The drug accountability log includes information such as, random number, amount dispensed and amount returned to the pharmacy (if any).

All dispensing and accountability records will be available for Sponsor review after database lock. When the Study Monitor visits the site, he or she will review the drug accountability log provided by the site pharmacy.

The site pharmacist (or designee under the direction of the pharmacist) will dispense IMP for each patient according to the protocol and pharmacy manual, if applicable.

After receiving Sponsor approval in writing, the site is responsible for returning all unused or partially used IMP to the Sponsor or designated third party or for preparing the IMP for destruction according to locally compliant procedures.

5.7. Patient Identification

5.7.1. Screening and Randomization Numbers

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 including the required improvement in disease activity will receive a randomization number on Day 1. The patient number (i.e. randomization number) will ensure identification throughout the study. The patient number will be assigned by a central telephone/world wide web based randomization system.

Patients dropping out or withdrawing, for any reason, without completing all screening evaluations successfully or who do not meet the requirements for improvement by Day 1 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 in order to assess the numbers and characteristics of the excluded patients, and the reasons for their exclusion.

5.8. Administration of Investigational Medicinal Product

XmAb5871 will be administered as an intravenous infusion over 1-2 hours (first infusion over 2 hours; subsequent infusions over 1-2 hours).

Study medication will be administered with the patient in a semi-supine position with the head of the bed elevated from 0 to 90 degrees. If an infusion chair is used, the patient's legs should be horizontal. For the initial infusion, patients are to remain fasted for at least 3 hours before starting the infusion until at least 1 hour after end of infusion. During pre-infusion fasting, no fluids are allowed except small amounts of water. During the post-dose fasting period, small amounts of clear liquids will be allowed. At subsequent infusions, patients should fast for 1 hour prior, may have small amounts of clear liquids during and after the infusion, and may resume their normal diet 1 hour later.

5.9. Compliance

Dosing will be performed by trained, qualified personnel designated by the PI. The date and time of dosing will be documented on each dosing day. Comments will be recorded if there are any deviations from the planned dosing procedures.

5.10. Concomitant Medications

5.10.1. Previous / Concomitant Medication

5.10.1.1. Disallowed previous or concomitant medications:

- Prior use of rituximab (or other B cell depleting agents) within 12 months of randomization or treatment with any other biologic therapeutics (including belimumab) within 6 months of randomization.
- Use of any investigational agent within 5 half-lives of the agent (or 6 months if the half-life is unknown) prior to randomization.
- Received live vaccines within 2 months of randomization.
- Immunosuppressive agents (e.g. methotrexate, azathioprine, mycophenolate mofetil, mycophenolic acid, leflunomide, cyclosporine, cyclophosphamide, tacrolimus, 6-mercaptopurine) will be stopped or tapered off during screening.
- Patients entering the study on oral corticosteroids (not to exceed the equivalent of 15 mg of prednisone per day – see Table 1) 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 remainder of the study.

Table 1: Prednisone Equivalence

Prednisone	10	mg
Hydrocortisone	40	mg
Prednisolone	10	mg
Triamcinolone	8	mg
Methylprednisolone	8	mg
Dexamethasone	1.5	mg
Betamethasone	1.2	mg
Cortisone acetate	50	mg

Details of all prior and concomitant medications will be recorded at study entry (i.e., at the first visit) including prior treatment for SLE, prior SLE clinical trial participation and prior monoclonal antibody use. All therapies (prescriptions or over-the-counter medications, including vitamins and herbal supplements) different from the study drug will be recorded in the eCRF. Any medicinal product, prescribed or OTC, including herbal and other non-traditional remedies, is considered a concomitant medication. Any changes in concomitant medication must be recorded at each visit whether or not prescribed by the study site. If the change might influence the patient's eligibility to continue in the study, the Sponsor

must be informed. Concomitant medication use may be warranted for the treatment of AEs. In the interests of patient safety and acceptable standards of medical care it is expected that the Investigator will prescribe treatment(s) at his/her discretion. All treatments must be recorded in the patients' case report form (CRF); medication, dose, treatment duration and indication.

The information collected for each concomitant medication includes, at a minimum, start date, end date or ongoing, dose and unit, frequency, route of administration and indication.

5.10.2. Contraception

Women are considered to be of childbearing potential unless there is a documented reason (i.e., postmenopausal by history with no menses for one year and confirmed by FSH [using local reference ranges], OR history of hysterectomy, OR history of bilateral tubal ligation, OR history of bilateral oophorectomy).

Women of childbearing potential must have a negative pregnancy test during screening and at Day 1 prior to study drug infusion and must use 1 highly effective method of birth control during the study and 3 months following last dose of XmAb5871. Highly effective methods of birth control include hormonal birth control, IUDs, or any barrier methods (sponges, female condoms) used by the woman in addition to contraception used by their male partner such as vasectomy or condom supplemented with spermicide.

Male patients of childbearing potential must be willing to practice a highly effective method of birth control for the duration of the study and continuing for 3 months after the last dose of XmAb5871. Highly effective methods of birth control include vasectomy or a condom in combination with barrier methods, hormonal birth control or IUD used by the woman.

6. VARIABLES AND METHODS OF ASSESSMENT

6.1. Safety Variables

Timing of assessments is shown in Table 6 Schedule of Assessments.

6.1.1. Medical History, Demographic and Other Baseline Information

The medical history comprises:

- General medical history including SLE history
- Medication history
- Reproductive history

The following demographic information will be recorded:

- Age
- Gender
- Ethnic origin (Hispanic/Latino or not Hispanic/not Latino)
- Race (White, American Indian/Alaska Native, Asian, Native Hawaiian or other Pacific Islander, Black/African American)
- Height, without shoes (in cm)
- Body weight, without shoes (in kg)
- Body mass index

6.1.2. Adverse Events

Adverse event reporting will begin upon the signing of the informed consent document and will continue until the last study visit.

6.1.2.1. Definitions

An AE is any untoward medical occurrence in a study patient administered an IMP which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP. Adverse events may include the onset of new illness and the exacerbation of pre-existing conditions.

Other untoward events occurring in the framework of a clinical study will be recorded as AEs, e.g., those occurring during treatment-free periods (including Screening or post-treatment Follow-up periods), in association with study-related procedures and assessments, or under placebo. For investigational products or placebo, lack of efficacy is an expected potential outcome and should not be reported as an AE unless the event is unusual in some way, e.g., greater in severity than the usual course of disease in a given patient.

Concomitant illnesses, which existed prior to entry into the clinical study, will not be considered AEs unless they worsen during the treatment period. Pre-existing conditions will be recorded as part of the patient's medical history.

Clinically significant abnormal laboratory results which are not caused by the underlying disease or are not consistent with the patient's medications will be recorded as AEs and the relationship

to the study drug will be indicated as in Table 3. Laboratory values outside the normal range will be assigned one of the following categories by the Investigator or designee:

1. Not clinically significant, minor out of range value/finding. AE - No
2. Not clinically significant, out of range value/finding explainable by anticipated or known effect of study drug or concomitant drugs. AE - No
3. Clinically significant but consistent with the patient's underlying disease. AE - No
4. Clinically significant out of range value/finding that does not fulfill categories 1-3. AE - Yes

6.1.2.2. Recording of Adverse Events

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

Adverse events may be volunteered spontaneously by the study patient, or discovered by the study staff during physical examinations or by asking an open, non-leading question such as 'How have you been feeling since you were last asked?' All AEs and any required remedial action will be recorded. The nature of AE, date (and time, if known) of AE onset, date (and time, if known) of AE outcome to date, severity, and action taken of the AE will be documented together with the Investigator's assessment of the seriousness of the AE and causal relationship to study drug and/or study procedure.

All AEs should be recorded individually in the study patient's own words (verbatim) unless, in the opinion of the Investigator, the AEs constitute components of a recognized condition, disease or syndrome. In the latter case, the condition, disease or syndrome should be named rather than each individual symptom. The AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA).

6.1.2.3. Assessment of Adverse Events

Each AE will be assessed by the Investigator with regard to the categories discussed in the sections below.

6.1.2.3.1. Intensity

The Investigator will assess all AEs for severity utilizing the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) grading scale (V 4.03). AEs not contained within CTCAE version 4.3 will be rated on a five-point scale (see Table 2):

Table 2: Severity Grading Scale

Mild (Grade 1)	Mild events are those which are easily tolerated with no disruption of normal daily activity.
Moderate (Grade 2)	Moderate events are those which cause sufficient discomfort to interfere with daily activity.
Severe (Grade 3)	Severe events are those which incapacitate and prevent usual activity.
Life-threatening (Grade 4)	An adverse event that has life-threatening consequences; for which urgent intervention is indicated; that puts the patient at risk of death at the time of the event if immediate intervention is not undertaken; or that causes blindness or deafness.
Fatal (Grade 5)	The termination of life as a result of an adverse event.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted for that day. Any change in severity of signs and symptoms over a number of days will be captured by recording a new AE, with the amended severity grade and the date (and time, if known) of the change.

6.1.2.3.2. Causality

The Investigator will assess the causality/relationship between the IMP and the AE. One of the following categories should be selected based on good medical and scientific judgment, considering the definitions below and all contributing factors (see Table 3).

Table 3: Causality Grading Scale

Related	A clinical event, including laboratory test abnormality, occurs in a plausible time relationship to treatment administration, and which concurrent disease or other drugs or chemicals cannot explain. The response to withdrawal of the treatment (dechallenge*) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge† procedure if necessary.
Probably Related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
Possibly Related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, but which could also be explained by concurrent disease or other drugs or chemicals. Information on treatment withdrawal may be lacking or unclear.
Unlikely Related	A clinical event, including laboratory test abnormality, with a temporal relationship to treatment administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
Not Related	A clinical event, including laboratory test abnormality, with little or no temporal relationship with treatment administration. May have negative dechallenge and rechallenge information. Typically explained by extraneous factors (e.g. concomitant disease, environmental factors or other drugs or chemicals)

***** Dechallenge is when a drug suspected of causing an AE is discontinued. If the symptoms of the AE disappear partially or completely, within a reasonable time from drug discontinuation, this is termed a positive dechallenge. If the symptoms continue despite withdrawal of the drug, this is termed a negative dechallenge. Note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists (for example, as in bone marrow suppression, fixed drug eruptions, or tardive dyskinesia).

† Rechallenge is when a drug suspected of causing an AE in a specific patient in the past is readministered to that patient. If the AE recurs upon exposure, this is termed a positive rechallenge. If the AE does not recur, this is termed a negative rechallenge.

6.1.2.3.3. Action Taken

Action taken will be defined as:

- None;
- Infusion interrupted;
- Infusion discontinued;
- Medication given (details to include medication name, start date and time, stop date and time, dose, route, frequency and reason for administration);
- Other (details of other to be specified)

6.1.2.3.4. Outcome

Outcome will be defined as:

- Death related to adverse event;
- Not recovered or not resolved;
- Recovered or resolved;
- Recovered or resolved with sequelae;
- Recovering or resolving;
- Unknown.

6.1.2.3.5. Seriousness

An SAE is defined as any untoward medical occurrence that occurs at any dose if it:

- Results in death;
- Is life-threatening; this means that the patient was at immediate risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe;
- Requires hospitalization or prolongation in existing hospitalization;
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Is a congenital anomaly or birth defect;
- Is an important medical event (see below).

Important medical events that do not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or in a physician's office, blood dyscrasias or seizures that do not result in in-patient hospitalization, and the development of drug dependency or drug abuse.

A distinction should be drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes would be considered an SAE, but is not necessarily severe. Similarly, an AE that is severe in intensity is not necessarily an SAE. For example, alopecia may be assessed as severe in intensity but would not be considered an SAE.

Medical and scientific judgment should be exercised in deciding if an AE is serious and if expedited reporting is appropriate.

6.1.2.3.6. Adverse Events of Special Interest

Infusion-related Reactions

All monoclonal antibody therapeutics are associated with the risk of both non-allergic (cytokine release syndrome) and allergic (hypersensitivity) infusion-related reactions.

A. Non-allergic reactions (cytokine release): Most infusion-related reactions are mild and non-allergic in etiology and may be alleviated by interruption of the infusion and reinitiating the infusion at the same of slower infusion rate after symptoms abate. Signs/symptoms may include: arthralgia (joint pain); cough; dizziness; dyspnea (shortness of breath); fatigue (asthenia, lethargy, malaise); fever; headache; hypertension; hypotension; myalgia (muscle pain); nausea; rash/desquamation; rigors/chills; sweating (diaphoresis); tachycardia; vomiting.

B. Allergic (hypersensitivity) reactions and anaphylaxis. The Immune System Disorders section of NCI-CTCAE 4.03 should be used to help characterize AEs related to hypersensitivity and immunogenicity. To identify cases of anaphylaxis in this study, the National Institute of Allergy and Infectious Diseases (NIAID) definition of anaphylaxis (Sampson et al 2006) will be used (see Table 4):

Table 4: Definition of Anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) *AND AT LEAST ONE OF THE FOLLOWING* a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) **b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)**
2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours): a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula) b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence) d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours): a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP* b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline
PEF = Peak expiratory flow; BP = blood pressure. *Low systolic blood pressure for children is defined as less than 70 mmHg from 1 month to 1 year, less than (70 mmHg + [2 × age]) from 1 to 10 years, and less than 90 mmHg from 11 to 17 years.

Monitoring during infusions

Patients should be closely monitored during and after infusion. XmAb5871 should be administered intravenously at a constant rate over a 1-2 hour period (2 hours for first infusion, 1-2 hours for subsequent infusions). Patients will be continuously assessed during the 1-2 hour infusion and for 1 hour following the end of infusion (2 hours following the first infusion). Vital signs including blood pressure, heart rate, respiratory rate and temperature assessments will be made within 2 hours prior to infusion, 30, 60 and 120 minutes from the start of infusion, at the end of infusion (if different than 120 minutes from start of infusion) and 30 and 60 minutes after end of infusion. During the first infusion, an additional measurement of vital signs should be made at 15 minutes after the start of infusion and after the end.

Severe infusion-related reactions, including deaths following the administration of otherwise well-tolerated monoclonal antibodies, have been reported rarely. As with all monoclonal IV antibody therapies, XmAb5871 should only be administered by healthcare providers and in healthcare settings that are prepared to recognize and to manage severe infusion-related reactions and/or anaphylaxis that can be life-threatening. All investigators should be well trained in the management of anaphylaxis (and other acute infusion-related events) including administration of epinephrine and other therapeutic modalities. Medications and equipment for the treatment of life-threating anaphylaxis should be available in the immediate area of treatment.

Management of Infusion-Related Reactions & Cytokine Release Syndrome

Infusion-related reactions and cytokine release syndrome will be toxicity graded according to the NCI-CTCAE, Version 4.3, as defined in Table 5.

Table 5: Infusion-Related Reaction and Cytokine Release Syndrome

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Infusion related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening; consequences; pressor or ventilatory support indicated

REMARK: An acute infusion-related reaction may occur with an agent that causes cytokine release (e.g., monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hrs of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Urticaria (hives, welts, wheals); Vomiting.

The Xencor Medical Monitor should be contacted immediately if questions arise concerning the grade of the infusion-related reaction.

An ADA sample should be drawn at the time of any suspected immunological related AE and at the time of each subsequent visit X 4 (and as per pre-specified sampling schedule).

The following are treatment guidelines for XmAb5871 treatment-related infusion-related reactions:

Grade 1 or 2:

- Discontinue the infusion and administer acetaminophen and/or diphenhydramine and/or dexamethasone to treat signs and symptoms if clinically indicated. Once symptoms have resolved, slow the infusion rate by 50% of the baseline rate. If, after one hour, the patient's symptoms do not return and vital signs are stable, the infusion rate may be increased every 30 minutes as tolerated to the baseline rate.
- Vital signs should be measured every 15 minutes or less as clinically indicated. For patients who are able to tolerate an increase in the infusion rate back to baseline and maintain normal blood pressure for 30 minutes after the rate increase then, at the discretion of the investigator, the frequency of vital sign assessment may be reduced to every 30 minutes during the infusion.
- Monitor the patient for worsening of condition; if severity of event increases to a higher Grade (Grade 3, or 4) stop the infusion, administer appropriate treatment, and refer to guidelines below for Grades 3 or 4 infusion-related reactions.
- Patients with maximum Grade 2 infusion-related reaction may continue on study and should receive prophylactic pre-medication with acetaminophen 650 mg po and diphenhydramine hydrochloride 25-50 mg IV and dexamethasone 10 mg IV (or equivalent) prior to all subsequent XmAb5871 infusions.

Grade 3 and 4:

- Stop the infusion and disconnect the infusion tubing from the patient.
- Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10-20 mg IV (or equivalent), and other medications/treatment as medically indicated.
- Give epinephrine or bronchodilators as indicated.
- Hospital admission for observation may be indicated.
- Patients with Grade 3 or 4 infusion-related reaction or with anaphylaxis should not receive further XmAb5871 treatment, but will continue to be followed on the protocol.
- Obtain blood sample for cytokine analysis during the event and approximately 24 hours later.
- Notify the Xencor Medical Monitor immediately.

Infusion-Associated Gastrointestinal-Related Symptoms

In the completed XmAb5871 single-dose FIH study, the most frequently reported treatment-related AEs were: nausea (7/36 subjects [19.4%]), vomiting (5/36 subjects [13.9%]), diarrhea (4/36 subjects [11.1%]) and abdominal pain (3/36 subjects [8.3%]) which typically occurred during the infusion. Symptoms were reported over the dose range of 0.2 to 10.0 mg/kg and at a similar overall level in each dose group. In the 8 cases of nausea and vomiting in which the IMP infusion was interrupted, the symptoms responsible for the interruption resolved quickly and no concomitant medication was required for relief of symptoms. When vomiting occurred, symptoms resolved very rapidly following the vomiting episode (1-3 minutes). The planned infusion was completed without recurrence of symptoms. No subject was withdrawn and none self-withdrew.

In the Phase 2a study in RA patients, 9 patients (23%) had their first XmAb5871 IV infusion temporarily interrupted as a result of the gastrointestinal symptoms (vomiting/nausea or diarrhea). Seven of the 9 (78%) occurred in the 10.0 mg/kg cohorts. In all but one episode, the symptoms were mild to moderate (one episode of severe vomiting). In all cases, the patients were able to continue the infusion after a short break (5-31 minutes) and symptoms did not recur on continuation of the infusion or during subsequent infusions. No concomitant medication was required for alleviation of symptoms.

There is no known mechanism of action by which a mAb with enhanced binding to FcγRIIb would result in infusion-associated, transient GI toxicity seen. There is also no known mechanism of action by which targeting CD19, a B cell restricted antigen, would produce such toxicity.

Mild to moderate nausea, vomiting or diarrhea may occur during the first infusion of XmAb5871. The patient should be monitored during the infusion and at the first sign of abdominal distress be allowed to elevate the head of the bed to up to a 90 degree position. Should nausea occur and become significant and/or vomiting occurs, the IV infusion should be interrupted. After a 15-30 minute interruption and if the patient's symptoms have substantially resolved, the infusion may be restarted at the original infusion rate.

6.1.2.4. Reporting of Serious Adverse Events

The Investigator will review each potential SAE and evaluate the intensity and the causal relationship of the event to IMP. All potential SAEs will be recorded from signing of informed consent until EOS. Serious AEs occurring after EOS and coming to the attention of the

Investigator must be reported only if there is (in the opinion of the Investigator) reasonable causal relationship with the IMP.

The Investigator is responsible for providing notification to Vigilare of any potential SAE, whether deemed IMP-related or not, that a patient experiences during their participation in study within 24 hours of becoming aware of the event. Vigilare will provide the information to the Sponsor.

As a minimum requirement, the initial notification should provide the following information:

- Study number
- Patient number
- Gender
- Date of birth
- Name of PI and full clinical site address
- Name of the reporter
- Details of SAE
- Criterion for classification as 'serious'
- Study drug name, dose and treatment start date
- Date of SAE onset
- Date of SAE first awareness (by Investigator or study site staff)
- Causality assessment

Vigilare will request clarification of omitted or discrepant information from the initial notification. The PI or an authorized delegate is responsible for providing the requested information to Vigilare within 24 hours of the request.

Initial reports of SAEs must be followed up as soon as possible with detailed descriptions; this may include clear photocopies of other documents as necessary (e.g., hospital reports, consultant reports, autopsy reports, etc.), with the study patient's personal identifiers removed. All relevant information obtained by the Investigator through review of these documents will be recorded and forwarded to Vigilare within 24 hours of receipt of the information. If a new SAE Report Form is completed, then the PI must sign and date the form. Vigilare and/or the Sponsor may also

request additional information on the SAE in order to obtain the full clinical picture, which the PI or an authorized delegate must respond to Vigilare within 24 hours of the request.

SERIOUS ADVERSE EVENT REPORTING INSTRUCTIONS

SAEXmAb5871-04@vigilareintl.com

24 hour telephone number: 610-977-0899 x4801

Emergency contact number: 917-741-5205

1. E-mail your SAE form to the study specific e-mail address above.
2. Provide Vigilare with the name of the PI, your name, the telephone number where you can be reached and the protocol number and title.
3. Immediately forward the SAE form and any supporting documentation to Vigilare: this must be done within 24 hours of becoming aware of the event.

6.1.2.5. Follow-up of Adverse Events

All AEs experienced by a patient, irrespective of the suspected causality, will be monitored until the event has resolved or stabilized, until any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the Investigator and Sponsor medical representative, until there is a satisfactory explanation for the changes observed, or until the patient is lost to Follow-up.

6.1.2.6. Pregnancy

The Investigator and Sponsor have a responsibility to monitor the outcome of all pregnancies, including pregnancies in partners of male participants, reported during the clinical study.

Pregnancy alone is not regarded as an AE unless there is a suspicion that the IMP may have interfered with the effectiveness of a contraceptive medication. 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. All notifications of pregnancy should be documented and reported whether or not there is an associated AE or SAE.

Each pregnancy notification must be reported by the Investigator to the Sponsor and Vigilare within 30 days after becoming aware of the pregnancy. In the event of pregnancy in a female participant, no more study drug will be given. However, the Investigator must follow-up and document the course and the outcome of all pregnancies if possible even if the patient was

withdrawn from the clinical study or if the clinical study has finished. The follow-up period will be deemed to have ended when the health status of the child has been determined on its birth.

All outcomes of pregnancy must be reported by the Investigator to the Sponsor and Vigilare on the pregnancy outcome report form within 30 days after he/she has gained knowledge of the normal delivery or elective abortion.

Any SAE that occurs during pregnancy must be recorded on the SAE report form (e.g., maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported within 24 hours of awareness in accordance with the procedure for reporting SAEs.

6.1.3. 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 siting position. The following vital signs will be measured:

- Blood pressure (systolic and diastolic [mmHg]);
- Heart rate (beats per minute [bpm]);
- Oral body temperature (°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.

6.1.4. 12-lead Electrocardiograms

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 ECG will include all 12 standard leads and a Lead II rhythm strip on the bottom of the tracing. The ECG will be recorded at a paper speed of 25 mm/sec. The following ECG parameters will be collected: PR interval, QRS interval, RR interval, QT interval, and QTc interval (QTcB and QTcF).

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

6.1.5. Physical Examinations

Physical examinations will be performed at Screening and on Days 1, 8, 29, 57, 85, 113, 141, 169, 197, 225 and 253(EOS).

The physical examination includes an assessment of general appearance and dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, neurologic, and psychiatric system evaluations.

6.1.6. Clinical Laboratory Assessments

Safety clinical laboratory assessments and flow cytometry for B cell and T cell quantitation and for CD19 RO will be performed by ICON Central Laboratories, Farmingdale, NY. PK and immunogenicity laboratory assessments will be performed by ICON Development Solutions, LLC, Whitesboro, NY. Genotyping will be performed by Cancer Genetics Inc., Morrisville, NC. Mechanistic studies will be done at Oklahoma Medical Research Foundation, Oklahoma City, OK.

Blood samples should be taken using standard venipuncture techniques. Blood sampling will be performed according to local SOPs.

The following laboratory variables will be determined as outlined below:

- **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 Day 1, 8, 29, 57, 85, 113, 141, 169, 197, 225 and 253(EOS): total protein, sodium, potassium, calcium, chloride, bicarbonate (HCO_3), 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.

- **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).
- **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).
- **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.
- **Serology**: HBsAg, HBcAb, and HCV Ab will be performed at Screening.
- **Urine pregnancy test**: Urine pregnancy testing will be performed in female patients at Screening, Days 1, 15, 43, 71, 99, 127, 155, 183, 211 and 253(EOS).
- **Follicle Stimulating Hormone (FSH)** will be performed in women of non-childbearing potential at Screening.
- **Immunogenicity:** The presence of human anti-human antibodies (ADA) will be assessed on Days 1, 15, 43, 85, 127, 183, 225 and 253(EOS).
- **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).

Mechanistic Studies:

For randomized patients, mechanistic studies that will be performed on Days 1, 29, and at the LOI visit (either at the visit at which loss of response is noted or on Day 225, whichever comes first) may include one or more of the following studies: BioPlex 2200 Autoantibody profiling, plasma cytokines by multiplex analysis and BioMark HD 96 gene RNA expression panel. Some or all of the following may also be measured: MMPs/TIMP levels, osteopontin, vonWillibrand's factor, and hsCRP, CXCL13, exosomal assays for numbers, size, function in patients with increased and suppressed disease activity, serum stimulation assays to assess ability to induce cytokine secretion, netosis, cell death pathways, and an expanded gene expression panel. Additional samples will be collected at screening and on Days 8, 15, 57, 71, 99, 113, 127, 141, 155, 169, 183, 197, 211 and 253(or EOS 6 weeks after loss of improvement, whichever comes first) and stored for potential mechanistic studies. Screening samples for all patients will be analyzed for ANA with pattern and anticardiolipin antibodies, with a repeat anticardiolipin antibody panel at LOI or Day 225, whichever comes first.

Blood requirements:

Blood will be collected for clinical laboratory testing as outlined below:

- Hematology: Blood (3 mL) will be collected into a lavender-top (EDTA) tube.
- Chemistry panel and FSH (if warranted): Blood (5.0 mL) will be collected into a serum gel (SST) tube.
- Hepatitis serologies (HBsAg, HBcAb, HCVAb): Blood (4.0 mL) will be collected into a serum gel (SST) tube.
- Coagulation panel: Blood (3.0 mL) will be collected into a blue top (Na Cit) tube.
- Immunoglobulins (IgG, IgM, IgE), Complement C3 and C4: Blood (5.0 mL) will be collected into a serum gel (STT) tube.
- SLE autoantibodies: Blood (4.0 mL) will be collected into a serum gel (SST) tube.
- XmAb5871 drug levels (PK; see section 6.2 below): Blood (5.0 mL) will be collected into a serum gel (SST) tube.
- Immunogenicity (ADA): Blood (5.0 mL) will be collected into a serum gel (SST) tube.
- Genotyping: Blood (8.5 mL) will be collected into a PAXgene™ Blood DNA collection tube.

- Flow Cytometry B Cell and T Cell Assessment: Blood (5 mL) will be collected into a Cyto-Chex BCT glass streck CE marked tube.
- Mechanistic Studies: Blood (25 mL) will be collected into one 10 mL SST tube, one 10 mL green top (heparin) tube and 2 RNA PAX gene tubes.

The total blood volume collected for clinical labs over the duration of the study will be approximately 770 mL over the course of the entire study, with approximately 50 mL collected per visit.

Laboratory Values Outside Normal Range:

Any value outside the normal range will be flagged for the attention of the Investigator or designee at the site. The Investigator or designee will indicate whether or not the value is of clinical significance as in Section 6.1.2.1. Laboratory values that are clinically significant 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.

6.2. Pharmacokinetic Variables

Blood (approximately 5.0 mL) will be collected at the following time points relative to XmAb5871 or placebo dosing: prior to the start of the infusion and at EOI on Study Days 1, 15, 29, 57, 85, 113, 141, and 155 and at visit time on Days 8, 225 and 253(EOS). The blood volume collected during the study for PK assessments will be approximately 95 mL. Blood sample collection, processing, and shipping details will be outlined in a separate laboratory manual. Samples will be processed and serum analyzed by a validated method for concentrations of XmAb5871. PK peak and trough values will be plotted over time.

6.3. Pharmacodynamic Variables

Pharmacodynamics of XmAb5871 will be evaluated by serial measurements, as outlined in Table 6 Schedule of Assessments, of absolute B cell counts (ABC) and B cell subsets, and CD19 receptor occupancy (RO).

6.4. Pharmacogenomics Variables

Blood will be collected as outlined as in Table 6 Schedule of Assessments on Day 1 (predose) for the assessment of FcγR genotype testing (FcγRIIa R131H and FcγRIIb I232T polymorphisms). The blood volume collected on Day 1 for the FcγR genotyping will be approximately 8.5 mL. Blood sample collection, processing, and shipping details will be

outlined in a separate laboratory manual. In brief, blood will be processed and the deoxyribonucleic acid (DNA) from the white blood cells will be analyzed for the FcγRIIa and FcγRIIb polymorphic alleles. Where patients provided informed consent, the residual FcγR polymorphism sample was retained by Xencor or Xencor's designee (below), 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.
133 Southcenter Court, Suite 400,
Morrisville, NC 27560,
USA

6.4.1. Efficacy Measurements

Disease activity will be measured at Screening and on Days 1, 29, 57, 85, 113, 141, 169, 197, 225 and 253(EOS). The following efficacy assessments will be performed according to the time points defined in Table 6 Schedule of Assessments:

SELENA SLEDAI

The SELENA SLEDAI is a tool designed to quantitate the amount of SLE disease activity a patient is experiencing at the present time (and in the proceeding 28 days). The instrument is intended to evaluate current SLE activity and not chronic damage, severity is accounted for in part by the "weightedness" of the scale. While it assesses the organs and systems commonly involved in SLE, it is weighted most heavily towards CNS and kidney involvement. The score will be recorded as the sum of descriptors present within the 28 days prior to the visit and visit day.

A sample assessment form is included in Appendix 11.1.1 and instructions for use are in Appendix 11.1.4.

BILAG

The British Isles Lupus Activity Group (BILAG) index assesses the month prior to the visit and is based on intent to treat logic. Organ systems are rated on whether the system has never been involved (E), has been involved in the past (D) but is not currently active, currently contains descriptor(s) which are mild (C), of moderate intensity (B), or severe in intensity (A). Each of the 9 systems receives an overall rating which incorporates the intensity and the change (if any) of each feature in that system during the past month.

A sample assessment form is included in Appendix 11.1.2 and instructions for use are in Appendix 11.1.4.

SELENA SLEDAI Physician Global Assessment Anchored VAS and SELENA SLEDAI Flare Index

The physician's overall assessment of the patient's current disease activity will be recorded on a 3 point (normalized to 100 mm) linear horizontal VAS, where the left hand extreme of the line is considered "none" (symptom free and no SLE symptoms) and the right hand extreme is considered "maximum" (maximum possible SLE activity). Anchors at "1" and "2" indicate increments for mild and moderate disease activity. The SELENA SLEDAI Flare Index combines changes (if any) in the Physician's Global Disease Activity with a variety of descriptors that define mild/moderate or severe flare.

A sample PGA form and SELENA SLEDAI Flare Index are included in Appendix 11.1.3.

7. STUDY CONDUCT

7.1. 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 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 Table 6 for the Schedule of Assessments.

7.1.1. Assessments by Visit

Please refer to Table 6 for a description of the assessments to be performed at each study visit.

7.1.2. Early Termination Visit

If a patient withdraws prematurely after dosing, assessments listed for the Day 225 visit should be performed at the time of loss of disease activity improvement or time of discontinuation for other reasons. 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 as a final safety check. Please see 7.1 above for those patients who experience a loss of improvement.

7.1.3. End-of-Study

End-of-Study is defined as completion of the End-of Study Visit on Day 253. For those patients who withdraw prematurely, EOS is defined as the time of the patient's last data collection.

Table 6: Schedule of Assessments [a]

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]						
FcγR 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.

8. STATISTICAL METHODS

Before database lock, a statistical analysis plan (SAP) will be issued as a separate document, providing detailed methods for the analyses and may supersede the analyses outlined below. Any deviations from the planned analyses will be described and justified in the final integrated clinical study report.

8.1. Study Population

8.1.1. Disposition of Patients

The number and percentage of patients screened, enrolled, randomized and completing the clinical study will be presented.

8.1.2. Protocol Deviations

Protocol deviations will be listed by patient.

8.1.3. Analysis Populations

The definitions of study populations are as follows:

- Enrolled Population: 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.
- Intent to Treat (ITT) Population: All patients who have received at least a partial dose of XmAb5871 or placebo.
- Efficacy Evaluable Population: 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)
- Safety Population: All patients who received at least a partial dose of XmAb5871 or placebo. In this study, this will be equivalent to the ITT population.
- Pharmacokinetic/Immunogenicity Population: All patients who received XmAb5871 and for whom the PK data are considered to be sufficient and interpretable will be included in the PK population. All patients who received XmAb5871 and have at least 1 post-IMP dosing ADA sample drawn will be included in the immunogenicity population.

- Pharmacodynamic Population: 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.

8.2. General Considerations

This is a randomized, double-blind, placebo-controlled study where descriptive and inferential statistics will be employed to analyze the data. Summary statistics for continuous variables will include the mean, standard deviation, median, and range (minimum/maximum); categorical variables will be presented as frequency counts and percentages; and time-to-event variables (if any) will be summarized by Kaplan-Meier methods (median, number censored, etc.) and Kaplan-Meier plots. Inferential statistical methodologies will be described below and data listings will be created to support each table and to present all data.

The data will be tabulated with respect to patient enrollment, patient disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, efficacy, and safety measures. The efficacy analysis will be performed on the Efficacy Evaluable and ITT Populations, and safety analysis on the Safety Population.

Prior to database lock, a statistical analysis plan (SAP) will be issued as a separate document that will provide additional detailed methods and mock table shells for the analyses outlined below. Any deviations from the planned analyses will be described and justified in the final integrated clinical study report.

8.3. Determination of Sample Size

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.

8.4. Treatment Assignment 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.

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 in order to assess the numbers and characteristics of the excluded patients, and the reasons for their exclusion.

8.5. Blinding

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.

8.6. Study Endpoints and Statistical Analyses

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.

8.6.1. 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 number of "responders" will be presented as frequency counts and percentages by treatment arm. The primary efficacy analysis will employ the Fisher's Exact Test testing for differences in treatment response rate (patients without loss of disease activity improvement from Day 1 to Day 225) between the two treatment groups. Exact confidence intervals will be computed for each treatment's binomial proportion of response.

8.6.2. 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 above.

The time to loss of SLE disease activity improvement achieved by a short period of IM steroid therapy in SLE patients 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.

8.6.3. Exploratory Efficacy Endpoints

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

- SELENA SLEDAI hybrid version with SELENA SLEDAI Flare index
- BILAG 2004
- Physician's Global Disease activity VAS

The SLEDAI, BILAG and PGA 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.

Additional analyses on exploratory parameters will be described in the SAP.

8.6.4. Safety and Tolerability Endpoints

Safety analyses will be performed using the Safety population (for this study is equivalent to ITT population).

- The number and percent of patients experiencing a treatment-emergent adverse event will be tabulated for each coded MedDRA system-organ class and preferred term by treatment arm. Treatment-emergent adverse events will also be tabulated according to intensity and causality by treatment arm.
- All serious adverse events, discontinuations due to adverse event, or deaths occurring during the course of the trial will be presented in patient listings.
- Clinical laboratory tests (observed values) will be summarized descriptively in tabular format by treatment arm. Shift tables will be presented for select laboratory parameters. In the patient listings, flags will be attached to values outside of the laboratory's reference limits along with the Investigator's assessment of clinical significance. A list of all normal laboratory ranges will also be provided. Clinically significant laboratory test abnormalities that were considered AEs by the Investigator will be presented in the AE listings.
- Vital signs (blood pressure, pulse, temperature) will be summarized (observed and change from baseline) at each visit vital signs are collected using descriptive statistics and patient listings.
- Twelve-lead ECG data (corrected QT intervals: Bazett's correction and Fridericia's correction) will be summarized (observed and change from baseline) by treatment arm at each visit ECGs are collected using descriptive statistics and patient listings.
- Concomitant Medications will be summarized by the number and percentage of patients in each therapeutic class and preferred term as coded using the WHODrug dictionary for each treatment arm.
- Physical Examinations will be presented in patient listings.

8.7. Pharmacokinetic Analyses

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).

8.8. Pharmacodynamic Analyses

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.

8.9. Pharmacokinetic/Pharmacodynamic Analyses

Individual and mean peak and trough serum concentrations of XmAb5871 will be plotted versus time on dual y-axis plots along with biomarkers CD19 RO, ABC, B cell subsets and anti-dsDNA antibody levels versus time. In addition, the change in peak and trough concentrations from baseline will be plotted versus time along with change from baseline in the biomarker measurements.

Direct comparison of PK versus PD will be done using scatterplots of peak and trough serum concentration versus PD biomarker value.

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.

8.10. Data Quality Assurance

Accurate, consistent, and reliable data will be ensured through the use Good Clinical Practices (GCP) guidelines regarding clinical data management practices and procedures.

8.11. Immunogenicity Analysis

Frequency and titer of anti-XmAb5871 antibodies (ADA) will be listed.

8.12. Interim Analyses

No formal interim analysis is planned, however aggregate blinded interim safety reviews may be performed for submission to regulatory authorities.

9. ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

9.1. Data Quality Assurance

The Sponsor will conduct a study initiation visit to verify the qualifications of the Investigator, inspect the facilities.

The Investigator must prepare and maintain adequate and accurate records of all observations and other data pertinent to the clinical study for each study participant. Frequent communication

between the clinical site and the Sponsor is essential to ensure that the safety of the study is monitored adequately. The Investigator will make all appropriate safety assessments on an ongoing basis. The Sponsor's medical representative will review safety information as it becomes available throughout the study.

All aspects of the study will be carefully monitored with respect to GCP and SOPs for compliance with applicable government regulations. The Study Monitor will be an authorized individual designated by PPD. The Study Monitor will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the PI.

The study may be audited to assess adherence to the Clinical Study Protocol. The Investigator/investigational site will permit study-related monitoring, audits, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and regulatory inspections by providing direct access to source data/documents. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical study.

During the conduct of the study, process-related audits may be performed as well. An audit certificate will be provided in the final study report outlining the audit performed and other related activities.

9.2. Access to Source Data/Documents

The Investigator will ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail will be maintained of all data changes. The Investigator or designee will cooperate with the Sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit.

Electronic consistency checks and manual review will be used to identify any errors or inconsistencies in the data. This information will be provided to the respective study sites by means of electronic or manual queries.

The Investigator or designee will prepare and maintain adequate and accurate study documents (medical records, ECGs, AE and concomitant medication reporting, raw data collection forms, etc.) designed to record all observations and other pertinent data for each patient receiving IMP.

The Investigator will allow Sponsor representatives, contract designees, authorized regulatory authority inspectors, and the Institutional Review Board (IRB) to have direct access to all documents pertaining to the study.

9.3. Archiving Study Documents

According to International Conference on Harmonization (ICH) guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. However, these documents should be retained for a longer period if required by the applicable legal requirements.

9.4. Good Clinical Practice

The procedures set out in this clinical study protocol are designed to ensure that the Sponsor and the Investigator abide by the principles of the ICH guidelines on Good Clinical Practice (GCP) as outlined in CPMP/ICH/135/95 and the Declaration of Helsinki (Version 2008). The clinical study also will be carried out in keeping with national and local legal requirements (in accordance with United States Investigational New Drug [IND] regulations [21 CFR Parts 50, 56 and 312]).

The Investigator will be responsible for the care of the patients throughout the study. If the Investigator is not present at the study site, he/she will leave instructions for the staff and contact information where he/she can be reached.

9.5. Informed Consent

Before each patient is enrolled in the clinical study, written informed consent will be obtained from the patient according to the regulatory and legal requirements of the participating country. 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 patient is aware of the potential risks, inconveniences, or AEs that may occur. The study patient 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 Principal 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 informed consent document must be signed and dated; one copy will be given to the patient, and the Investigator will retain a copy as part of the clinical study records. The Investigator will

not undertake any investigation specifically required for the clinical study until written consent has been obtained. The terms of the consent and when it was obtained must also be documented.

If a protocol amendment is required, then the informed consent document may need to be revised to reflect the changes to the protocol. If the informed consent document is revised, it must be reviewed and approved by the responsible IRB/Independent Ethics Committee (IEC), and signed by all patients subsequently enrolled in the clinical study as well as those currently enrolled in the clinical study.

9.6. Protocol Approval and Amendment(s)

Before the start of the clinical study, the clinical study protocol and other relevant documents will be approved by the IRB, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the clinical study.

This protocol is to be followed exactly. Any deviations should be agreed by both the Sponsor and the Investigator, with the appropriate written and approved protocol amendments made to reflect the changes agreed upon. Protocol amendments must be released by the responsible staff and must receive IRB approval prior to implementation. Where a protocol deviation occurs for the well-being of the patient, the Sponsor must be informed of the action. Any deviations and protocol violations that occur must be reported to the Sponsor and to the IRB as per local IRB requirements.

Administrative changes may be made without the need for a formal amendment, but will also be mentioned in the integrated clinical study report. All amendments will be distributed to all study protocol recipients, with appropriate instructions.

9.7. Confidentiality Data Protection

All clinical study findings and documents will be regarded as confidential. Study documents (protocols, IBs and other material) will be stored appropriately to ensure their confidentiality. The Investigator and members of his/her research team (including the IRB) must not disclose such information without prior written approval from the Sponsor, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial or to comply with regulatory requirements.

The anonymity of participating patients must be maintained. Patients will be specified on study documents by their patient number, initial or birth date, not by name. Documents that identify

the patient (e.g., the signed informed consent document) must be maintained in confidence by the Investigator.

9.8. Publication Policy

By signing the clinical study protocol, the Investigator agrees with the use of results of the clinical study for the purposes of national and international registration, publication and information for medical and pharmaceutical professionals. If necessary, the competent authorities will be notified of the Investigator's name, address, qualifications and extent of involvement.

An Investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted with the Sponsor in advance.

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11. APPENDICES

11.1. Efficacy Assessments

11.1.1. Hybrid SELENA SLEDAI and SELENA SLEDAI Flare Index

The Hybrid SELENA SLEDAI is a tool designed to detect amount of disease activity and identify improvements and worsening of disease.

Hybrid SELENA SLEDAI with SELENA SLEDAI FLARE INDEX and PGA

(Hybrid SLEDAI is the SELENA SLEDAI except using proteinuria definition from SLEDAI 2K)
(Circle in SLEDAI Score column if descriptor is present at the time of the visit or in the preceding 4 weeks)
(The same instrument can also be used going back only ten days)

Item no.	SLEDAI SCORE	Descriptor	Definition
1	**8**	**Seizure**	Recent onset, exclude metabolic, infectious or drug causes
2	**8**	**Psychosis**	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganised, or catatonic behaviour. Exclude uraemia and drug causes
3	**8**	**Organic brain syndrome**	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes
4	**8**	**Visual disturbance**	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudates or hemorrhages in the choroid, or optic neuritis, scleritis or episcleritis. Exclude hypertension, infection, or drug causes
5	**8**	**Cranial nerve disorder**	New onset of sensory or motor neuropathy involving cranial nerves
6	**8**	**Lupus headache**	Severe, persistent headache; may be migrainous, but must be non-responsive to narcotic analgesia THIS WOULD RARELY BE ATTRIBUTED TO SLE...ALMOST NEVER SCORED
7	**8**	**CVA**	New onset Cerebrovascular accident(s). Exclude arteriosclerosis
8	**8**	**Vasculitis**	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages or biopsy or angiogram proof of vasculitis
9	**4**	**Arthritis**	> 2 joints with pain and signs of inflammation (i.e. tenderness with swelling or effusion)
10	**4**	**Myositis**	Proximal muscle aching/weakness, associated with elevated creatinine phosphokinase (CK)/aldolase, or EMG changes or a biopsy showing myositis
11	**4**	**Urinary casts**	Heme-granular or RBC casts
12	**4**	**Hematuria**	> 5 RBC/high power field. Exclude stone, infection or other cause

13	**4**	**Proteinuria**	> 0.5 gram/24 hours
14	**4**	**Pyuria**	> 5 WBC/high power field. Exclude infection
15	**2**	**Rash**	Inflammatory type rash
16	**2**	**Alopecia**	Abnormal, patchy or diffuse loss of hair
17	**2**	**Mucosal ulcers**	Oral or nasal ulcerations
18	**2**	**Pleurisy**	Pleuritic chest pain or pleural rub or effusion, or pleural thickening (does not require an objective component if medically convincing)
19	**2**	**Pericarditis**	Classic pericardial pain and/or rub, effusion or ECG or echocardiogram confirmation (does not require an objective component if medically convincing)
20	**2**	**Low complement**	Decrease in CH50, C3 or C4 < lower limit of nl for testing laboratory
21	**2**	**Increased DNA binding**	Increased DNA binding above normal range for testing laboratory
22	**1**	**Fever**	> 38ºC. Exclude infectious cause
23	**1**	**Thrombocytopenia**	< 100×10^9 platelets/L, exclude drug causes
24	**1**	**Leukopenia**	< 3×10^9 WBC/L, exclude drug causes

_____ Total SCORE

CLASSIC SELENA SLEDAI FLARE INDEX (Can be used with any version of the SLEDAI)

Physician's Global Assessment (PGA)
Visual Analog Scale with anchors

0 1 2 3 (this was developed as a three inch scale but has been
None Mild Moderate Severe used in trials as a 100mm scale)

Mild or Moderate Flare □

□ Change in SELENA SLEDAI instrument score of 3 points or more (but not to more than 12)
□ New/worse: Discoid, photosensitive, profundus, bullous lupus,
- □ Nasopharyngeal ulcers
- □ Pleuritis
- □ Pericarditis
- □ Arthritis
- □ Cutaneous Vasculitis
- □ Fever (SLE)

□ Increase in prednisone, but not to >0.5 mg/kg/day
□ Added NSAID or hydroxychloroquine for SLE activity
□ ≥1.0 increase in PGA score, but not to more than 2.5

Severe Flare □

- Change in SELENA SLEDAI instrument score to greater than 12
- New/worse: CNS-SLE
  - cutaneous vasculitis,
  - Vasculitis
  - Nephritis
  - Myositis
- Plt <60,000
- Hemolytic anemia: Hb <70 g/L or decrease in Hb >30 g/L

Requiring: double prednisone, or prednisone increase to >0.5 mg/kg/day, or hospitalization

- Increase in prednisone to >0.5 mg/kg/day
- New cyclophosphamide, azathioprine, methotrexate for SLE activity
- Hospitalization for SLE activity
- Increase in Physician's Global Assessment score to >2.5

11.1.2. BILAG2004

BILAG2004 INDEX **Centre:** **Date:** **Initials/Hosp No:**

Only record items due to SLE Disease Activity & assessment refers to manifestations occurring in the last 4 weeks (compared with the previous 4 weeks). **♦♦ TO BE USED WITH THE GLOSSARY ♦♦**

Scoring: **ND** Not Done
1 Improving
2 Same
3 Worse
4 New
Yes/No OR Value (where indicated)
❑ indicate if not due to SLE activity
(default is 0 = not present)

CONSTITUTIONAL
1. Pyrexia - documented > 37.5°C ( )
2. Weight loss - unintentional > 5% ( )
3. Lymphadenopathy/splenomegaly ( )
4. Anorexia ( )

MUCOCUTANEOUS
5. Skin eruption - severe ( )
6. Skin eruption - mild ( )
7. Angio-oedema - severe ( )
8. Angio-oedema - mild ( )
9. Mucosal ulceration - severe ( )
10. Mucosal ulceration - mild ( )
11. Panniculitis/Bullous lupus - severe ( )
12. Panniculitis/Bullous lupus - mild ( )
13. Major cutaneous vasculitis/thrombosis ( )
14. Digital infarcts or nodular vasculitis ( )
15. Alopecia - severe ( )
16. Alopecia - mild ( )
17. Peri-ungual erythema/chilblains ( )
18. Splinter haemorrhages ( )

NEUROPSYCHIATRIC
19. Aseptic meningitis ( )
20. Cerebral vasculitis ( )
21. Demyelinating syndrome ( )
22. Myelopathy ( )
23. Acute confusional state ( )
24. Psychosis ( )
25. Acute inflammatory demyelinating polyradiculoneuropathy ( )
26. Mononeuropathy (single/multiplex) ( )
27. Cranial neuropathy ( )
28. Plexopathy ( )
29. Polyneuropathy ( )
30. Seizure disorder ( )
31. Status epilepticus ( )
32. Cerebrovascular disease (not due to vasculitis) ( )
33. Cognitive dysfunction ( )
34. Movement disorder ( )
35. Autonomic disorder ( )
36. Cerebellar ataxia (isolated) ( )
37. Lupus headache - severe unremitting ( )
38. Headache from IC hypertension ( )

MUSCULOSKELETAL
39. Myositis - severe ( )
40. Myositis - mild ( )
41. Arthritis (severe) ( )
42. Arthritis (moderate)/Tendonitis/Tenosynovitis ( )
43. Arthritis (mild)/Arthralgia/Myalgia ( )

Weight (kg): **Serum urea (mmol/l):**
African ancestry: Yes/No **Serum albumin (g/l):**

CARDIORESPIRATORY
44. Myocarditis - mild ( )
45. Myocarditis/Endocarditis + Cardiac failure ( )
46. Arrhythmia ( )
47. New valvular dysfunction ( )
48. Pleurisy/Pericarditis ( )
49. Cardiac tamponade ( )
50. Pleural effusion with dyspnoea ( )
51. Pulmonary haemorrhage/vasculitis ( )
52. Interstitial alveolitis/pneumonitis ( )
53. Shrinking lung syndrome ( )
54. Aortitis ( )
55. Coronary vasculitis ( )

GASTROINTESTINAL
56. Lupus peritonitis ( )
57. Abdominal serositis or ascites ( )
58. Lupus enteritis/colitis ( )
59. Malabsorption ( )
60. Protein losing enteropathy ( )
61. Intestinal pseudo-obstruction ( )
62. Lupus hepatitis ( )
63. Acute lupus cholecystitis ( )
64. Acute lupus pancreatitis ( )

OPHTHALMIC
65. Orbital inflammation/myositis/proptosis ( )
66. Keratitis - severe ( )
67. Keratitis - mild ( )
68. Anterior uveitis ( )
69. Posterior uveitis/retinal vasculitis - severe ( )
70. Posterior uveitis/retinal vasculitis - mild ( )
71. Episcleritis ( )
72. Scleritis - severe ( )
73. Scleritis - mild ( )
74. Retinal/choroidal vaso-occlusive disease ( )
75. Isolated cotton-wool spots (cytoid bodies) ( )
76. Optic neuritis ( )
77. Anterior ischaemic optic neuropathy ( )

RENAL
78. Systolic blood pressure (mm Hg) value ( ) ❑
79. Diastolic blood pressure (mm Hg) value ( ) ❑
80. Accelerated hypertension Yes/No ( )
81. Urine dipstick protein (+=1, ++=2, +++=3) ( ) ❑
82. Urine albumin-creatinine ratio mg/mmol ( ) ❑
83. Urine protein-creatinine ratio mg/mmol ( ) ❑
84. 24 hour urine protein (g) value ( ) ❑
85. Nephrotic syndrome Yes/No ( )
86. Creatinine (plasma/serum) µmol/l ( ) ❑
87. GFR (calculated) ml/min/1.73 m^2 ( ) ❑
88. Active urinary sediment Yes/No ( )
89. Active nephritis Yes/No ( )

HAEMATOLOGICAL
90. Haemoglobin (g/dl) value ( ) ❑
91. Total white cell count (x 10^9/l) value ( ) ❑
92. Neutrophils (x 10^9/l) value ( ) ❑
93. Lymphocytes (x 10^9/l) value ( ) ❑
94. Platelets (x 10^9/l) value ( ) ❑
95. TTP ( )
96. Evidence of active haemolysis Yes/No ( )
97. Coombs' test positive (isolated) Yes/No ( )

Revision: 6/Feb/2009

11.1.3. Physician Global Assessment of Disease Activity (VAS)

Physician's Global Assessment of Disease Activity (100 mm-VAS)

Place a mark on the line below to indicate disease activity:

Physician's Global Assessment (PGA)
Visual Analog Scale with anchors

0 1 2 3 (this was developed as a three inch scale but has been used in trials as a 100mm scale)
None Mild Moderate Severe

$VAS_{Physician\ Global\ Assessment\ of\ Disease\ Activity}$ = _____ mm

11.1.4. BILAG2004 and SELENA SLEDAI Instructions

GUIDELINES FOR USE OF THE SELENA SLEDAI MODIFIED FOR ASSESSMENT OVER 28 DAYS: TO ASSESS DISEASE ACTIVITY

General guidelines for the SELENA SLEDAI

(Hybrid Version using SLEDAI 2K Proteinuria Definition)

- The main principle to keep in mind is that this instrument is intended to evaluate current lupus activity and not chronic damage, severity is accounted for in part by the "weightedness" of the scale.
- Points are given exactly as defined.
- A descriptor is either scored the exact points allotted or not scored, i.e. given a zero. Descriptors are scored only if they are present at the time of the physician encounter or in the preceding 28 days. (The SLEDAI 2K instrument is validated both for the original use with a 10 day window and for the use of a 28 day window, and any of the SLEDAI versions can be used with a 28 day window). Small deviations in this window which are allowed in a clinical trial protocol for monthly visits are acceptable in scoring the SLEDAI. However, it is never acceptable to fill in gaps which cover activity over 2-3 months or more. The reason for this is that disease activity at the visit might have changed several times in such intervals and the recording of distant activity becomes meaningless.

  Please note that in the original SLEDAI the disease activity being scored was meant to cover only a ten day period, the modification to 28 days is a more useful assessment for use in clinical trials, in order to capture disease activity between monthly visits. However the SLEDAI does require documented confirmation of events that may have occurred and resolved between visits.
  It is critical to record all new events that have developed during this time, for which there are very convincing lupus symptoms and/or signs consistent with glossary definitions for

the items, even if the item has since disappeared. However, if a feature that was present at the last visit disappears soon after the last visit (within one week) then the item is not recorded on the SELENA SLEDAI form.

- The descriptors which are scored must be documented by the notes written in the physician encounter form. This rule generally applies to the clinical data and not to the laboratory data. The laboratory data is strictly defined as per cutoffs and documentation is provided by the reports from the commercial laboratory.
- Descriptors do not have to be new but can be. They can be ongoing, recurrent, or initial events. Each would be scored the same way. An example would be a malar rash or mucosal ulcer. In these situations a malar rash observed at the initial visit but which remains unchanged for the next six months, irrespective of any treatment, is scored 2 points each time the SLEDAI is completed. Since the nature of lupus is that clinically significant manifestations are not usually fleeting it would be rare for descriptors to be present during the month and not seen at the time of the encounter. This is discussed in more detail for each descriptor but is especially relevant for some neurologic, pulmonary, and cutaneous manifestations. A major exception would be seizure, due to lupus, which requires solid documentation but obviously would not need to be continuing at the time of the visit.
- In some descriptors the exclusions written may not be exhaustive. The intent of the SLEDAI is that the descriptor be attributed to SLE. If the physician does not attribute the descriptor to SLE it should not be scored, but documentation in support of this decision must be provided.

Written in italics is the definition for each descriptor precisely provided in the SLEDAI SCORE
SEIZURE

Definition: Recent onset (last 28 days). Exclude metabolic, infectious or drug cause, or seizure due to past irreversible CNS damage.

This descriptor is scored if the patient has had a witnessed seizure or convincing description (such as tongue biting or incontinence) within 30 days of the current encounter. The patient need not have a positive EEG, CT scan, PET scan, QEEG, or MRI. The CSF may be totally normal.

A seizure is also not counted:

1. If a metabolic cause is determined.
2. In the presence of a proven infectious meningitis, brain abscess, or fungal foci.
3. If there is a history of recent head trauma.
4. In the presence of an offending drug.
5. In the presence of severe hyperthermia or hypothermia.
6. If the patient has stopped taking anticonvulsant medication.
7. If the patient has a documented sub-therapeutic anticonvulsant drug level.

PSYCHOSIS

Definition: Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes.

This descriptor is scored if any of the criteria above are met.

With regard to drug causes the most problematic situation is glucocorticoids. If the treating physician attributes the psychosis to glucocorticoids this descriptor should not be counted.

ORGANIC BRAIN SYNDROME

Definition: Altered mental function with impaired orientation, memory or other intellectual function, with rapid onset and fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus, and inability to sustain attention to environment, plus at least two of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes.

a. reduced capacity to focus as exemplified by new inability to perform everyday mathematical computations or disorientation to person, place, time, or purpose

OR

b. inability to carry on a conversation

OR

c. reduction in short term memory

PLUS: Documented abnormality on neuropsychiatric testing

Neuropsychiatric testing may take the form of a "mini-mental-status exam" or a formal neuropsychiatric examination. The important aspect for scoring OBS is that it be reversible. Consideration should be given to the improvement of OBS after institution of glucocorticoids.

This descriptor is not scored in the presence of a metabolic, infectious, or drug cause. If the problem is chronic this descriptor is not scored in SLEDAI but is scored on the damage index.

VISUAL DISTURBANCE

Definition: Retinal and eye changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, optic neuritis, scleritis or episcleritis. Exclude hypertension, infection or drug causes.

This is scored exactly as defined with the understanding that it must be supported by objective evidence.

CRANIAL NERVE DISORDER

Definition: New onset of sensory or motor neuropathy involving cranial nerves. Include vertigo due to lupus.

This is scored exactly as defined with the understanding that it must be supported by objective evidence. However, it should be noted that hydroxychloroquine can affect the eighth cranial nerve.

LUPUS HEADACHE

Definition: Severe persistent headache: may be migrainous, but must be non-responsive to narcotic analgesia.

For this descriptor to be counted, the headache must be present for greater than 24 hours and must not be responsive to narcotic analgesia. Objective documentation need not be present although it is expected that such a complaint, given the severity, would prompt formal testing such as MRI, CT, LP, etc. Furthermore, the headache should be of sufficient severity to warrant the initiation of glucocorticoids or additional immunosuppressive agents. Scoring of this descriptor means attribution of the headache to CNS lupus.

Most headaches, including most severe and/or migrainous headaches are not attributable to lupus and this descriptor should only be scored very rarely.

CVA

Definition: New onset of cerebrovascular accident (s). Exclude arteriosclerosis or hypertensive causes.

This descriptor is scored if the patient has had a CVA within 28 days of the current encounter. A patient recovering from a CVA that was documented more than 28 days prior to the current encounter is not given points for this descriptor. A patient may have had a previous CVA but to be scored the current CVA must be new.

This descriptor is scored in the presence or absence of anti-phospholipid antibodies, i.e., the precise pathophysiologic mechanism need not be known.

The CVA is scored even in the presence of a normal CT or MRI. A TIA is also scored if the patient gives a convincing history. To exclude atherosclerosis the patient has to have a normal carotid and/or vertebral Doppler and cannot have uncontrolled hypertension.

VASCULITIS

Definition: Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.

To score this descriptor the above definitions must be present. For example, erythematous lesions on the hands or feet which may be characteristically considered "leukocytoclastic vasculitis" but do not fulfill at least one of the above definitions and if not biopsied, are not

counted. Similarly livedo reticularis is not counted. Healed ulcers with residual scar are not to be counted, but be sure to count these in the damage index. A lesion consistent with erythema nodosum should be counted regardless of whether it is biopsied or not. Purpura in the presence of a normal platelet count should be counted regardless of whether it has been biopsied or not.

ARTHRITIS

Definition: More than two joints with pain and signs of inflammation, i.e., tenderness, swelling, or effusion.

Arthritis is scored if it is ongoing; it need not be new or recurrent.

Arthritis is scored only if *more than two* joints manifest signs of inflammation. For example if only the right second and left third PIPs are involved or only both wrists, points for this descriptor are not given.

Inflammation is strictly defined in this activity index as the **presence of tenderness** (the patient complains of pain on palpating the joint or upon going through range of motion) **PLUS** any one of the following:

1. swelling
2. effusion
3. warmth
4. erythema, but must exclude overlying cellulitis

The presence of tenderness alone is not sufficient. A patient's complaints of pain in specific joints without objective findings is not sufficient. An exception would be arthritis of the hip in which case pain in the groin on range of motion accompanied by decreased range of motion in the absence of swelling, warmth, or erythema would be counted. Inflammation of the tendons, ligaments, bursae, and other periarticular structures are not scored. For example subacromial bursitis and trochanteric bursitis are not scored. If further evaluation reveals osteonecrosis or osteoarthritis, this descriptor is not counted.

MYOSITIS

Definition: Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.

The patient complains of muscle aching and/or weakness in the proximal muscles PLUS one of the following must be present:

1. elevated serum creatine phosphokinase and/or aldolase
2. abnormalities on electromyogram consistent with myositis
3. biopsy-proven myositis

URINARY CASTS

Definition: Heme-granular or red blood cell casts.

This is scored if red blood cell casts are seen, even if it is only one. Pigmented casts are counted but non-pigmented granular casts, hyaline or waxy casts are not counted.

HEMATURIA

Definition: >5 red blood cells/high power field. Exclude stone, infection or other cause.

With regard to this descriptor, every attempt should be made to see patients when they are not menstruating. If this is not possible the urinalysis should be deferred until the next visit.

This descriptor is not scored if there is documented renal calculi or infection. The latter must be confirmed by a positive urinary culture. However it is acknowledged that associated conditions such as chlamydia or urethral irritation may result in mild hematuria and the physician's best judgment is warranted. **The important point is attribution: there must be other evidence of nephritis and other causes of hematuria must be excluded.**

In the complete absence of proteinuria, attribution of hematuria to active nephritis would be very unlikely unless pathology is limited to the mesangium.

PROTEINURIA

Definition: more than 0.5 g/24 hours attributed to lupus nephritis.

PYURIA

Definition: >5 white blood cells/high power field. Exclude infection.

This descriptor is not scored if there is evidence of vaginal contamination (presence of any squamous epithelial cells) or a documented infection. The latter must be confirmed by a positive urinary culture. However, it is acknowledged that associated conditions such as chlamydia, trichomonas or urethral irritation may result in mild pyuria and the physician's best judgment is warranted. **The important point is attribution; there must be other evidence of nephritis, and other causes of pyuria should be excluded.** In the complete absence of proteinuria, attribution of hematuria to active nephritis would be very unlikely unless pathology is limited to the interstitium.

RASH

Definition: <u>Ongoing</u> inflammatory lupus rash.

A rash is scored if it is ongoing, new or recurrent. Even if it is identical in terms of distribution and character to that observed on the last visit and the intensity is improved, it is counted. Therefore, despite improvement in a rash, if it is still ongoing it represents disease activity. The rash must be attributable to SLE. A description of the rash must appear in the physical exam and should include distribution, characteristics such as macular or papular, and size.

The following should not be scored:

1. Chronic scarred discoid plaques in any location.
2. Transient malar flush, i.e., it is not raised and is evanescent

A common problem one may encounter is the differentiation between scoring a lesion as "rash" and/or "vasculitis". If a lesion meets the descriptive criteria of the latter it should not also be counted as rash, i.e., the score would be 8 points not 10 points. If a separate rash characteristic of SLE is present only then would "rash" also be scored.

ALOPECIA:

Definition: Ongoing abnormal, patchy or diffuse loss of hair due to active lupus.

This should be scored if any of the following conditions are present:

1. There is temporal thinning which is newly present for less than six months (if temporal alopecia is present for more than six months with no change it should not be counted)
2. Areas of scalp with total bald spots if present for less than six months (does not need to have accompanying discoid lesion or follicular plugging)
3. The presence of "lupus frizz" i.e., short of strands of unruly hair in the frontal or temporal area

If a patient complains of hair loss and there is nothing apparent on exam this descriptor is not scored.

MUCOSAL ULCERS:

Definition: <u>Ongoing</u> oral or nasal ulcerations due to active lupus.

An ulcer is scored if it is ongoing, it need not be new or recurrent. Ulcers can be present in either the nose or oral cavity. Erythema alone without frank ulceration is not sufficient to be scored, even if the erythema is present on the upper palate. Ulcers on the buccal mucosa and tongue are counted.

Mucosal ulcers are not counted as vasculitis.

PLEURISY

Definition: Classic and severe pleuritic chest pain or pleural rub or effusion or new pleural thickening due to lupus.

This descriptor is scored if the patient complains of pleuritic chest pain lasting greater than 12 hours. The pain should be classic, i.e., exacerbated by inspiration, to help distinguish it from musculoskeletal conditions such as costochondritis, which could be confused with pleurisy. The symptom does not have to be accompanied by any objective findings. The presence of objective findings such as pleural rub or pleural effusions (in the absence of infection, congestive heart failure, malignancy, or nephrosis) is counted, even if not accompanied by symptoms. New pleural thickening should be counted only if other causes as described above are absent.

PERICARDITIS:

Definition: Classic and severe pericardial pain or rub or effusion, or electrocardiogram, or echo confirmation.

The symptom does not have to be accompanied by objective findings.

LOW COMPLEMENT:

Definition: Decrease in CH50, C3 or C4 below the lower limit of normal for testing laboratory.

Exclude a low C4 or CH50 in patients with known inherited deficiency of C4.

INCREASED DNA BINDING

Definition: >25% binding by Farr assay or above normal range for testing laboratory.

FEVER:

Definition: >38°C. Exclude infectious cause.

This would be scored if one of the following conditions are present:

1. A documented temperature elevation >100.4°F or >38°C at the time of the visit.
2. A convincing history from the patient that she/he has been febrile within the preceding 10 days prior to the visit without any signs or symptoms suggestive of infection. Febrile is defined as above and not simply that the patient felt feverish. In this case the patient need not be febrile at the time of the visit for a score of 2 to be given.

As stated in the SLEDAI, fever secondary to infection is not to be scored although it is acknowledged that concomitant lupus activity and infection can occur. Fever in the presence of infection should only be scored on the SLEDAI if other evidence of lupus activity is present.

THROMBOCYTOPENIA:

Definition: <100,000 platelets/mm^3.

LEUKOPENIA:

Definition: <3,000 white blood cells/mm^3. Exclude drug causes.

This is exactly as described, WBC <3,000/mm^3. The presence of an absolute lymphopenia does not count in the SLEDAI. A note of caution, do not confuse this WBC with that used to satisfy the ACR criteria for SLE which is WBC <3,500/mm^3.

With regard to current use of possible offending drugs, the following guidelines are to be considered:

1. The nadir after cyclophosphamide, i.e., low WBC at 10 days after receiving cyclophosphamide in a patient known to have a WBC ≥ 3,000 at the time of receiving cyclophosphamide should not be counted.
2. Do not score leukopenia appearing after initiation of a new medication known to be associated with leukopenia, such as azathioprine or sulfa drugs. If the patient develops a WBC <3000 while taking drugs which may cause leukopenia, score this only if the dosage of medication is unchanged since the last WBC determination.

CLASSIC SELENA SLEDAI FLARE INDEX (SFI) instructions

THE SELENA SLEDAI FLARE INDEX RULES ARE FOLLOWED EXPLICITLY AS WRITTEN. HOWEVER THERE ARE SOME CLARIFICATIONS TO KEEP IN MIND WHEN USING THE SELENA SLEDAI COMPOSITE INDEX.

Instructions for using the SELENA SLEDAI Physicians Global Assessment Scale

This PGA is a modification of the classic analogue scale in that it is anchored with numbers from 0-3 demarcating mild, moderate and severe disease. Please note several things about this scale. The number 3 indicates severe disease and is at the very end of the scale. This refers to the most severe possible disease, and does not reflect the most severe ever seen in a particular patient but the most severe disease ever seen in all SLE patients. Therefore, the line made by the physician along this scale should virtually never get to this edge. Any disease rated greater than 2.5 is very severe. The range of moderate disease covers about 1.5-2.4. Mild disease falls below 1.5. Clearly, this is a bit like a logarithmic scale with greater distances or demarcations possible among more mild-moderate symptoms. This needs to be kept in mind when scoring the instrument.

When scoring the PGA always look back at the score from the previous visit and move the mark relative to that previous visit. This is a global assessment, factoring in all aspects of the patients lupus disease activity. It should not reflect non-lupus medical conditions.

These instructions are quite discrete from those given for other analogue (Lichert) scales and are specific for the scoring of the SELENA SLEDAI PGA.

When is a flare not a flare?

It is important to keep in mind that on the SELENA SLEDAI flare index flare can be defined simply by a decision to institute new therapy for lupus disease activity, whether or not the patient meets the other criteria for flare listed. It is important for the physician not to override the intent of the instrument which is to actually define flare in this manner. However there are logical exceptions, for which a common sense rule may prevail. Switching treatments for safety reasons, or increasing treatment in patients who are improving might often warrant withdrawal from a protocol. However if the protocol allows these medication changes, the flare index will need to be scored, but it does not make sense to call these situations flares.

BILAG-2004 INDEX GLOSSARY

INSTRUCTIONS

- only record features that are **attributable to SLE disease activity and not due to damage, infection, thrombosis (in absence of inflammatory process) or other conditions**
- assessment refers to manifestations occurring in the **last 4 weeks compared with the previous 4 weeks**
- activity refers to disease process which is reversible while damage refers to permanent process/scarring (irreversible)
- damage due to SLE should be considered as a cause of features that are fixed/persistent (SLICC/ACR damage index uses persistence ≥ 6 months to define damage)
- in some manifestations, it may be difficult to differentiate SLE from other conditions as there may not be any specific test and the decision would then lies with the **physician's judgment on the balance of probabilities**
- ophthalmic manifestations usually need to be assessed by an ophthalmologist and these items would need to be recorded after receiving the response from the ophthalmologist
- guidance for scoring:

(4) NEW

- manifestations are recorded as new when it is a new episode occurring in the last 4 weeks (compared to the previous 4 weeks) that has not improved and this includes new episodes (recurrence) of old manifestations
- new episode occurring in the last 4 weeks but also satisfying the criteria for improvement (below) would be classified as improving instead of new

(3) WORSE

- this refers to manifestations that have deteriorated in the last 4 weeks compared to the previous 4 weeks

(2) SAME

- this refers to manifestations that have been present for the last 4 weeks and the previous 4 weeks without significant improvement or deterioration (from the previous 4 weeks)
- this also applies to manifestations that have improved over the last 4 weeks compared to the previous 4 weeks but do not meet the criteria for improvement

(1) IMPROVING

- definition of **improvement**: (a) the amount of improvement is sufficient for **consideration of reduction in therapy** and would not justify escalation in therapy

AND

(b) improvement must be **present currently and for at least 2 weeks** out of the last 4 weeks

OR

manifestation that has **completely resolved and remained absent** over the **whole of last 1 week**

(0) NOT PRESENT

(ND) NOT DONE

- it is important to indicate if a test has not been performed (particularly laboratory investigations) so that this will be recorded as such in the database & not as

normal or absent (which is the default)

❑ **INDICATE (TICK) IF NOT DUE TO SLE ACTIVITY**

- for descriptors that are based on measurements (in renal and haematology systems), it is important to indicate if these are not due to lupus disease activity (for consideration of scoring) as they are usually recorded routinely into a database

CHANGE IN SEVERITY CATEGORY

- there are several items in the index which have been divided into categories of mild and severe (depending on definition). It is essential to record mild and severe items appropriately if the manifestations fulfil both criteria during the last 4 weeks

- if a mild item deteriorated to the extent that it fulfilled the definition of severe category (ie changed into severe category) within the last 4 weeks:
  severe item scored as new (4)
  AND mild item scored as worsening (3)

- if a severe item improved (fulfilling the improvement criteria) to the extent that it no longer fulfilled the definition of severe category (ie changed into mild category) within the last 4 weeks:
  severe item scored as not present (0) if criteria for severe category has not been met over last 4 weeks
  or as improving (1) if criteria for severe category has been met at some point over last 4 weeks

AND

mild item scored as improving (1) if it is improving over last 4 weeks
or as the same (2) if it has remained stable over last 4 weeks

CONSTITUTIONAL

1. Pyrexia temperature > 37.5˚C documented
2. Unintentional weight loss > 5%
3. Lymphadenopathylymph node more than 1 cm diameter
   exclude infection
4. Anorexia

MUCOCUTANEOUS

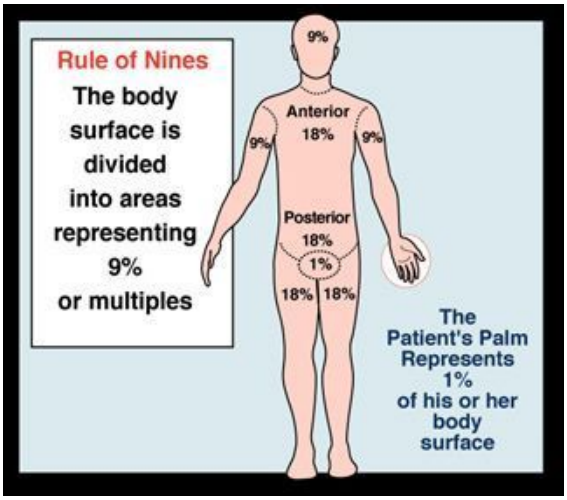
5. Severe eruption > 18% body surface area

any lupus rash except panniculitis, bullous lesion & angio-oedema

body surface area (BSA) is estimated using the rules of nines (used to assess extent of burns) as follows:

palm(excluding fingers) = 1% BSA
each lower limb = 18% BSA
each upper limb = 9% BSA
torso (front) = 18% BSA
torso (back) = 18% BSA

head = 9% BSA
genital (male) = 1% BSA



6. Mild eruption ≤ 18% body surface area

any lupus rash except panniculitis, bullous lesion & angio-oedema

malar rash must have been observed by a physician and has to be present continuously (persistent) for at least 1 week to be considered significant (to be recorded)

7. Severe angio-oedema

potentially life-threatening eg: stridor

angio-oedema is a variant form of urticaria which affects the subcutaneous, submucosal and deep dermal tissues

8. Mild angio-oedema

not life threatening

9. Severe mucosal ulceration

disabling (significantly interfering with oral intake), extensive & deep ulceration

must have been observed by a physician

10. Mild mucosal ulceration

localised &/or non-disabling ulceration

11. Severe panniculitis or bullous lupus

any one: > 9% body surface area

facial panniculitis

panniculitis that is beginning to ulcerate

panniculitis that threatens integrity of subcutaneous tissue (beginning to cause surface depression) on > 9% body surface area, panniculitis presents as a palpable and tender subcutaneous induration/nodule

note that established surface

	depression and atrophy alone is likely to be damage
12. Mild panniculitis or bullous lupus	≤ 9% body surface area does not fulfil any criteria for severe panniculitis
13. Major cutaneous vasculitis/thrombosis	resulting in extensive gangrene or ulceration or skin infarction
14. Digital infarct or nodular vasculitis	localised single or multiple infarct(s) over digit(s) or tender erythematous nodule(s)
15. Severe alopecia	clinically detectable (diffuse or patchy) hair loss with scalp inflammation (redness over scalp)
16. Mild alopecia	diffuse or patchy hair loss without scalp inflammation (clinically detectable or by history)
17. Peri-ungual erythema or chilblains	chilblains are localised inflammatory lesions (may ulcerate) which are precipitated by exposure to cold
18. Splinter haemorrhages	

NEUROPSYCHIATRIC

19. Aseptic meningitis criteria (all):	acute/subacute onset headache fever abnormal CSF (raised protein &/or lymphocyte predominance) but negative cultures preferably photophobia, neck stiffness and meningeal irritation should be present as well but are not essential for diagnosis, exclude CNS/meningeal infection, intracranial haemorrhage
20. Cerebral vasculitis should be present with features of vasculitis in another system	supportive imaging &/or biopsy findings
21. Demyelinating syndrome	discrete white matter lesion with associated neurological deficit not recorded elsewhere ideally there should have been at least one previously recorded event supportive imaging required exclude multiple sclerosis
22. Myelopathy	acute onset of rapidly evolving paraparesis or quadriparesis and/or sensory level exclude intramedullary and extramedullary space occupying lesion
23. Acute confusional state	acute disturbance of consciousness or level of arousal with reduced ability to focus, maintain or shift attention

	includes hypo- and hyperaroused states and encompasses the spectrum from delirium to coma
24. Psychosis delusion or hallucinations	does not occur exclusively during course of a delirium exclude drugs, substance abuse, primary psychotic disorder
25. Acute inflammatory demyelinating criteria:	polyradiculoneuropathy progressive polyradiculoneuropathy loss of reflexes symmetrical involvement increased CSF protein without pleocytosis supportive electrophysiology study
26. Mononeuropathy (single/multiplex)	supportive electrophysiology study required
27. Cranial neuropathy	except optic neuropathy which is classified under ophthalmic system
28. Plexopathy	disorder of brachial or lumbosacral plexus resulting in neurological deficit not corresponding to territory of single root or nerve supportive electrophysiology study required
29. Polyneuropathy	acute symmetrical distal sensory and/or motor deficit supportive electrophysiology study required
30. Seizure disorder	independent description of seizure by reliable witness
31. Status epilepticus	a seizure or series of seizures lasting ≥ 30 minutes without full recovery to baseline
32. Cerebrovascular disease	any one with supporting imaging: (not due to vasculitis) stroke syndrome transient ischaemic attack intracranial haemorrhage exclude hypoglycaemia, cerebral sinus thrombosis, vascular malformation, tumour, abscess cerebral sinus thrombosis not included as definite thrombosis not considered part of lupus activity
33. Cognitive dysfunction	significant deficits in any cognitive functions: simple attention (ability to register & maintain information) complex attention memory (ability to register, recall & recognise information eg learning, recall) visual-spatial processing (ability to analyse, synthesise & manipulate visual-spatial information) language (ability to comprehend, repeat & produce oral/written material eg verbal fluency, naming) reasoning/problem solving (ability to reason & abstract) psychomotor speed executive functions (eg planning, organising, sequencing)

	in absence of disturbance of consciousness or level of arousal sufficiently severe to interfere with daily activities neuropsychological testing should be done or corroborating history from third party if possible exclude substance abuse
34. Movement disorder	exclude drugs
35. Autonomic disorder any one:	
	fall in blood pressure to standing > 30/15 mm Hg (systolic/diastolic)
	increase in heart rate to standing ≥ 30 bpm
	loss of heart rate variation with respiration (max – min < 15 bpm, expiration:inspiration ratio < 1.2, Valsalva ratio < 1.4)
	loss of sweating over body and limbs (anhidrosis) by sweat test
	exclude drugs and diabetes mellitus
36. Cerebellar ataxia	cerebellar ataxia in isolation of other CNS features
	usually subacute presentation
37. Severe lupus headache (unremitting)	disabling headache unresponsive to narcotic analgesia & lasting ≥ 3 days
	exclude intracranial space occupying lesion and CNS infection
38. Headache from IC hypertension	exclude cerebral sinus thrombosis

MUSCULOSKELETAL

39. Severe myositis	significantly elevated serum muscle enzymes with significant muscle weakness
	exclude endocrine causes and drug-induced myopathy
	electromyography and muscle biopsy are used for diagnostic purpose and are not required to determine level of activity
40. Mild myositis	significantly elevated serum muscle enzymes with myalgia but without significant muscle weakness
	asymptomatic elevated serum muscle enzymes not included
	exclude endocrine causes and drug-induced myopathy

	electromyography and muscle biopsy are used for diagnostic purpose and are not required to determine level of activity
41. Severe arthritis	observed active synovitis ≥ 2 joints with marked loss of functional range of movements and significant impairment of activities of daily living, that has been present on several days (cumulatively) over the last 4 weeks
42. Moderate arthritis or Tendonitis or Tenosynovitis	tendonitis/tenosynovitis or active synovitis ≥ 1 joint (observed or through history) with some loss of functional range of movements, that has been present on several days over the last 4 weeks
43. Mild arthritis or Arthralgia or Myalgia	inflammatory type of pain (worse in the morning with stiffness, usually improves with activity & not brought on by activity) over joints/muscle inflammatory arthritis which does not fulfil the above criteria for moderate or severe arthritis

CARDIORESPIRATORY

44. Mild myocarditis	inflammation of myocardium with raised cardiac enzymes &/or ECG changes and without resulting cardiac failure, arrhythmia or valvular dysfunction
45. Cardiac failure	cardiac failure due to myocarditis or non-infective inflammation of endocardium or cardiac valves (endocarditis) cardiac failure due to myocarditis is defined by left ventricular ejection fraction ≤ 40% & pulmonary oedema or peripheral oedema cardiac failure due to acute valvular regurgitation (from endocarditis) can be associated with normal left ventricular ejection fraction diastolic heart failure is not included
46. Arrhythmia	arrhythmia (except sinus tachycardia) due to myocarditis or non-infective inflammation of endocardium or cardiac valves (endocarditis) confirmation by electrocardiogram required (history of palpitations alone inadequate)
47. New valvular dysfunction	new cardiac valvular dysfunction due to myocarditis or non-infective inflammation of endocardium or cardiac valves (endocarditis) supportive imaging required
48. Pleurisy/Pericarditis	convincing history &/or physical findings that you would consider treating

	in absence of cardiac tamponade or pleural effusion with dyspnoea do not score if you are unsure whether or not it is pleurisy/pericarditis
49. Cardiac tamponade	supportive imaging required
50. Pleural effusion with dyspnea	supportive imaging required
51. Pulmonary haemorrhage/vasculitis	inflammation of pulmonary vasculature with haemoptysis &/or dyspnoea &/or pulmonary hypertension supportive imaging &/or histological diagnosis required
52. Interstitial alveolitis/pneumonitis	radiological features of alveolar infiltration not due to infection or haemorrhage required for diagnosis corrected gas transfer Kco reduced to < 70% normal or fall of > 20% if previously abnormal on-going activity would be determined by clinical findings and lung function tests, and repeated imaging may be required in those with deterioration (clinically or lung function tests) or failure to respond to therapy
53. Shrinking lung syndrome	acute reduction (> 20% if previous measurement available) in lung volumes (to < 70% predicted) in the presence of normal corrected gas transfer (Kco) & dysfunctional diaphragmatic movements
54. Aortitis	inflammation of aorta (with or without dissection) with supportive imaging abnormalities accompanied by > 10 mm Hg difference in BP between arms &/or claudication of extremities &/or vascular bruits repeated imaging would be required to determine on-going activity in those with clinical deterioration or failure to respond to therapy
55. Coronary vasculitis	inflammation of coronary vessels with radiographic evidence of non-atheromatous narrowing, obstruction or aneurysmal changes
GASTROINTESTINAL	
56. Lupus peritonitis	serositis presenting as acute abdomen with rebound/guarding
57. Serositis	not presenting as acute abdomen
58. Lupus enteritis or colitis	vasculitis or inflammation of small or large bowel with supportive imaging &/or biopsy findings
59. Malabsorption	diarrhoea with abnormal D- xylose absorption test or increased faecal fat excretion after exclusion of coeliac's disease (poor response to gluten-free diet) and gut vasculitis

60. Protein-losing enteropathy	diarrhoea with hypoalbuminaemia or increased faecal excretion of IV radiolabeled albumin after exclusion of gut vasculitis and malabsorption
61. Intestinal pseudo-obstruction	subacute intestinal obstruction due to intestinal hypomotility
62. Lupus hepatitis	raised transaminases absence of autoantibodies specific to autoimmune hepatitis (eg: anti-smooth muscle, anti-liver cytosol 1) &/or biopsy appearance of chronic active hepatitis hepatitis typically lobular with no piecemeal necrosis exclude drug-induced and viral hepatitis
63. Acute lupus cholecystitis	after exclusion of gallstones and infection
64. Acute lupus pancreatitis	usually associated multisystem involvement

OPHTHALMIC

65. Orbital inflammation	orbital inflammation with myositis &/or extra-ocular muscle swelling &/or proptosis supportive imaging required
66. Severe keratitis	sight threatening includes: corneal melt peripheral ulcerative keratitis
67. Mild keratitis	not sight threatening
68. Anterior uveitis	
69. Severe posterior uveitis &/or retinal vasculitis	sight-threatening &/or retinal vasculitis not due to vaso-occlusive disease
70. Mild posterior uveitis &/or retinal vasculitis	not sight-threatening not due to vaso-occlusive disease
71. Episcleritis	
72. Severe scleritis	necrotising anterior scleritis, anterior &/or posterior scleritis requiring systemic steroids/immunosuppression &/or not responding to NSAIDs
73. Mild scleritis	anterior &/or posterior scleritis not requiring systemic steroids excludes necrotising anterior scleritis
74. Retinal/choroidal disease	vaso-occlusive includes: retinal arterial & venous occlusion serous retinal &/or retinal pigment epithelial detachments secondary to choroidal vasculopathy

75. Isolated cotton-wool spots	also known as cytoid bodies
76. Optic neuritis	excludes anterior ischaemic optic neuropathy
77. Anterior ischaemic optic neuropathy	visual loss with pale swollen optic disc due to occlusion of posterior ciliary arteries

RENAL

78. Systolic blood pressure	
79. Diastolic blood pressure	
80. Accelerated hypertension	blood pressure rising to > 170/110 mm Hg within 1 month with grade 3 or 4 Keith-Wagener-Barker retinal changes (flame-shaped haemorrhages or cotton-wool spots or papilloedema)
81. Urine dipstick	
82. Urine albumin-creatinine ratio	on freshly voided urine sample conversion: 1 mg/mg = 113 mg/mmol it is important to exclude other causes (especially infection) when proteinuria is present
83. Urine protein-creatinine ratio	on freshly voided urine sample conversion: 1 mg/mg = 113 mg/mmol it is important to exclude other causes (especially infection) when proteinuria is present
84. 24 hour urine protein	it is important to exclude other causes (especially infection) when proteinuria is present
85. Nephrotic syndrome criteria:	heavy proteinuria (≥ 3.5 g/day or protein-creatinine ratio ≥ 350 mg/mmol or albumin-creatinine ratio ≥ 350 mg/mmol) hypoalbuminaemia oedema
86. Plasma/Serum creatinine	exclude other causes for increase in creatinine (especially drugs)
87. GFR MDRD formula:	$GFR = 170 \times [\text{serum creatinine (mg/dl)}]^{-0.999} \times [\text{age}]^{-0.176} \times [\text{serum urea (mg/dl)}]^{-0.17} \times [\text{serum albumin (g/dl)}]^{0.318} \times [0.762 \text{ if female}] \times [1.180 \text{ if African ancestry}]$ units = ml/min per 1.73 m^2 normal: male = 130 ± 40 female = 120 ± 40 conversion:

	serum creatinine - mg/dl = (μmol/l)/88.5 serum urea - mg/dl = (mmol/l) × 2.8 serum albumin - g/dl = (g/l)/10
	creatinine clearance not recommended as it is not reliable
	exclude other causes for decrease in GFR (especially drugs)
88. Active urinary sediment	pyuria (> 5 WCC/hpf or > 10 WCC/mm^3 (μl)) OR haematuria (> 5 RBC/hpf or > 10 RBC/mm^3 (μl)) OR red cell casts OR white cell casts exclude other causes (especially infection, vaginal bleed, calculi)
89. Histology of active nephritis	WHO Classification (1995): (any one) Class III – (a) or (b) subtypes Class IV – (a), (b) or (c) subtypes Class V – (a), (b), (c) or (d) subtypes Vasculitis OR ISN/RPS Classification (2003): (any one) Class III – (A) or (A/C) subtypes Class IV – (A) or (A/C) subtypes Class V Vasculitis within last 3 months glomerular sclerosis without inflammation not included
HAEMATOLOGICAL	
90. Haemoglobin	exclude dietary deficiency & GI blood loss
91. White cell count	exclude drug-induced cause
92. Neutrophil count	exclude drug-induced cause
93. Lymphocyte count	
94. Platelet count	exclude thrombocytopenia of antiphospholipid syndrome & drug-induced cause
95. TTP	thrombotic thrombocytopaenic purpura clinical syndrome of micro-angiopathic haemolytic anaemia and thrombocytopenia in absence of any other identifiable cause

96. Evidence of active haemolysis	positive Coomb's test & evidence of haemolysis (raised bilirubin or raised reticulocyte count or reduced haptoglobulins)

97. Isolated positive Coomb's test

ADDITIONAL ITEMS

These items are required mainly for calculation of GFR

i. Weight
ii. African ancestry
iii. Serum urea
iv. Serum albumin

BILAG-2004 INDEX SCORING

- scoring based on the principle of physician's intention to treat

Category	Definition
A	**Severe disease activity requiring any of the following treatment:** **1. systemic high dose oral glucocorticoids (equivalent to prednisolone > 20 mg/day)** **2. intravenous pulse glucocorticoids (equivalent to pulse methylprednisolone ≥ 500 mg)** **3. systemic immunomodulators (include biologicals, immunoglobulins and plasmapheresis)** **4. therapeutic high dose anticoagulation in the presence of high dose steroids or immunomodulators** **eg: warfarin with target INR 3 - 4**
B	**Moderate disease activity requiring any of the following treatment:** **1. systemic low dose oral glucocorticoids (equivalent to prednisolone ≤ 20 mg/day)** **2. intramuscular or intra-articular or soft tissue glucocorticoids injection (equivalent to methylprednisolone < 500mg)** **3. topical glucocorticoids** **4. topical immunomodulators** **5. antimalarials or thalidomide or prasterone or acitretin** **6. symptomatic therapy** **eg: NSAIDs for inflammatory arthritis**
C	**Mild disease**
D	**Inactive disease but previously affected**
E	**System never involved**

CONSTITUTIONAL

CATEGORY A:

Pyrexia recorded as 2 (same), 3 (worse) or 4 (new) **AND**

Any 2 or more of the following recorded as 2 (same), 3 (worse) or 4 (new):

Weight loss
Lymphadenopathy/splenomegaly

Anorexia

CATEGORY B:
Pyrexia recorded as 2 (same), 3 (worse) or 4 (new) **OR**

Any 2 or more of the following recorded as 2 (same), 3 (worse) or 4 (new):

Weight loss
Lymphadenopathy/splenomegaly
Anorexia

BUT do not fulfil criteria for Category A

CATEGORY C
Pyrexia recorded as 1 (improving) **OR**

One or more of the following recorded as > 0:

Weight loss
Lymphadenopathy/Splenomegaly
Anorexia

BUT does not fulfil criteria for category A or B

CATEGORY D
Previous involvement

CATEGORY E
No previous involvement

MUCOCUTANEOUS

CATEGORY A
Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Skin eruption - severe
Angio-oedema - severe
Mucosal ulceration - severe
Panniculitis/Bullous lupus - severe
Major cutaneous vasculitis/thrombosis

CATEGORY B
Any Category A features recorded as 1 (improving) **OR**

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Skin eruption - mild
Panniculitis/Bullous lupus - mild
Digital infarcts or nodular vasculitis
Alopecia - severe

CATEGORY C
Any Category B features recorded as 1 (improving) **OR**

Any of the following recorded as > 0:

Angio-oedema - mild
Mucosal ulceration - mild
Alopecia - mild
Periungual erythema/chilblains
Splinter haemorrhages

CATEGORY D
Previous involvement

CATEGORY E
No previous involvement

NEUROPSYCHIATRIC

CATEGORY A
Any of the following recorded as 2 (same), 3 (worse) or 4 (new):
Aseptic meningitis
Cerebral vasculitis
Demyelinating syndrome
Myelopathy
Acute confusional state
Psychosis
Acute inflammatory demyelinating polyradiculoneuropathy
Mononeuropathy (single/multiplex)
Cranial neuropathy
Plexopathy
Polyneuropathy
Status epilepticus
Cerebellar ataxia

CATEGORY B
Any Category A features recorded as 1 (improving) OR Any of the following recorded as 2 (same), 3 (worse) or 4 (new):
Seizure disorder
Cerebrovascular disease (not due to vasculitis)
Cognitive dysfunction
Movement disorder
Autonomic disorder
Lupus headache - severe unremitting
Headache due to raised intracranial hypertension

CATEGORY C
Any Category B features recorded as 1 (improving)

CATEGORY D
Previous involvement

CATEGORY E
No previous involvement

MUSCULOSKELETAL

CATEGORY A
Any of the following recorded as 2 (same), 3 (worse) or 4 (new):
Severe Myositis
Severe Arthritis

CATEGORY B
Any Category A features recorded as 1 (improving)
OR
Any of the following recorded as 2 (same), 3 (worse) or 4 (new):
Mild Myositis
Moderate Arthritis/Tendonitis/Tenosynovitis

CATEGORY C
Any Category B features recorded as 1 (improving) OR Any of the following recorded as > 0: Mild Arthritis/Arthralgia/Myalgia

CATEGORY D
Previous involvement

CATEGORY E
No previous involvement

CARDIORESPIRATORY

CATEGORY A
Any of the following recorded as 2 (same), 3 (worse) or 4 (new):
Myocarditis/Endocarditis + Cardiac failure
Arrhythmia
New valvular dysfunction
Cardiac tamponade
Pleural effusion with dyspnea
Pulmonary haemorrhage/vasculitis
Interstitial alveolitis/pneumonitis
Shrinking lung syndrome
Aortitis
Coronary vasculitis

CATEGORY B
Any Category A features recorded as 1 (improving) OR Any of the following recorded as 2 (same), 3 (worse) or 4 (new):
Pleurisy/Pericarditis
Myocarditis – mild

CATEGORY C
Any Category B features recorded as 1 (improving)

CATEGORY D
Previous involvement

CATEGORY E
No previous involvement

GASTROINTESTINAL

CATEGORY A
Any of the following recorded as 2 (same), 3 (worse) or 4 (new):
Peritonitis
Lupus enteritis/colitis
Intestinal pseudo-obstruction

Acute lupus cholecystitis
Acute lupus pancreatitis

CATEGORY B
Any Category A feature recorded as 1 (improving) OR Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Abdominal serositis and/or ascites
Malabsorption
Protein losing enteropathy
Lupus hepatitis

CATEGORY C
Any Category B features recorded as 1 (improving)

CATEGORY D
Previous involvement

CATEGORY E
No previous involvement

OPHTHALMIC

CATEGORY A
Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Orbital inflammation/myositis/proptosis
Keratitis - severe
Posterior uveitis/retinal vasculitis - severe
Scleritis - severe
Retinal/choroidal vaso-occlusive disease
Optic neuritis
Anterior ischaemic optic neuropathy

CATEGORY B
Any Category A features recorded as 1 (improving) **OR**
Any of the following recorded as 2 (same), 3 (worse) or 4 (new):
Keratitis - mild

Anterior uveitis
Posterior uveitis/retinal vasculitis - mild
Scleritis – mild

CATEGORY C
Any Category B features recorded as 1 (improving) **OR**

Any of the following recorded as > 0:

Episcleritis
Isolated cotton-wool spots (cytoid bodies)

CATEGORY D
Previous involvement

CATEGORY E
No previous involvement

RENAL

CATEGORY A

Two or more of the following providing 1, 4 or 5 is included:
1. Deteriorating proteinuria (severe) defined as
(a) urine dipstick increased by ≥ 2 levels (used only if other methods of urine protein estimation not available); **or**
(b) 24 hour urine protein > 1 g that has not decreased (improved) by ≥ 25%; **or**
(c) urine protein-creatinine ratio > 100 mg/mmol not decreased (improved) by ≥ 25%; **or**
(d) urine albumin-creatinine ratio > 100 mg/mmol not decreased (improved) by ≥ 25%
2. Accelerated hypertension
3. Deteriorating renal function (severe) defined as
(a) plasma creatinine > 130 μmol/l and having risen to > 130% of previous value; **or**
(b) GFR < 80 ml/min per 1.73 m^2 and having fallen to < 67% of previous value; **or**
(c) GFR < 50 ml/min per 1.73 m^2, and last time was > 50 ml/min per 1.73 m^2 or not done
4. Active urinary sediment
5. Histological evidence of active nephritis within last 3 months
6. Nephrotic syndrome

CATEGORY B
One of the following:
1. One of the Category A features
2. Proteinuria (that has not fulfilled Category A criteria)
(a) urine dipstick which has risen by 1 level to at least 2+ (used only if other methods of urine protein estimation not available); **or**
(b) 24 hour urine protein ≥ 0.5 g that has not decreased (improved) by ≥ 25%; **or**
(c) urine protein-creatinine ratio ≥ 50 mg/mmol not decreased (improved) by ≥ 25%; **or**
(d) urine albumin-creatinine ratio ≥ 50 mg/mmol that has not decreased (improved) by ≥ 25%
3. Plasma creatinine > 130 μmol/l and having risen to ≥ 115% but ≤ 130% of previous value

CATEGORY C
One of the following:
1. Mild/Stable proteinuria defined as
(a) urine dipstick ≥ 1+ but has not fulfilled criteria for Category A & B (used only if other methods of urine protein estimation not available); **or**
(b) 24 hour urine protein > 0.25 g but has not fulfilled criteria for Category A&B ; **or**
(c) urine protein-creat ratio > 25 mg/mmol but has not fulfilled criteria for Category A&B; **or**
(d) urine albumin-creatinine ratio > 25 mg/mmol not fulfilled criteria for Category A & B
2. Rising blood pressure (providing the recorded values are > 140/90 mm Hg) which has not fulfilled criteria for Category A & B, defined as
(a) systolic rise of ≥ 30 mm Hg; **and**
(b) diastolic rise of ≥ 15mm Hg

CATEGORY D
Previous involvement

CATEGORY E
No previous involvement

Note: although albumin-creatinine ratio and protein-creatinine ratio are different, we use the same cut-off values for this index

HAEMATOLOGICAL

CATEGORY A
TTP recorded as 2 (same), 3 (worse) or 4 (new) **OR** Any of the following:
Haemoglobin < 8 g/dl
White cell count < 1.0×10^9/l

Neutrophil count < 0.5×10^9/l
Platelet count < 25×10^9/l

CATEGORY B
TTP recorded as 1 (improving) **OR**

Any of the following:
Haemoglobin 8 - 8.9 g/dl
White cell count 1 - 1.9×10^9/l
Neutrophil count 0.5 - 0.9×10^9/l
Platelet count 25 - 49×10^9/l
Evidence of active haemolysis

CATEGORY C
Any of the following:
Haemoglobin 9 - 10.9 g/dl
White cell count 2 - 3.9×10^9/l
Neutrophil count 1 - 1.9×10^9/l
Lymphocyte count < 1.0×10^9/L
Platelet count 50 - 149×10^9/l
Isolated Coombs' test positive

CATEGORY D OR E
Previous involvement or no Previous involvement respectively

Definition of Flare Using the BILAG 2004 Index

- Severe Flare: A score due to item(s) recorded as 4 for new or 3 for worse
- Moderate Flare: 2 or more B scores due to items recorded as 4 for new or 3 for worse
- Mild Flare: 1B or $\geq$3 C scores due to item(s) recorded as 4 for new or 3 for worse

The increase in disease activity should be severe enough in all cases such that an increase in treatment, commensurate with the severity level chosen, would be appropriate. However it is not necessary that the treatment actually be started, given that there are too many variables in what the patient may have recently started that has not had time to take effect, or treatment withholding due to current infections, side effects, compliance etc.