Clinical Study Protocol

An Open-label, Single-arm, Pilot Study to Evaluate the Effect of XmAb®5871 on Disease Activity in Patients with IgG4-Related Disease

Sponsor:	Xencor, Inc. 111 West Lemon Avenue Monrovia, CA 91016
Clinical Research Organization:	The Translational Medicine Group Massachusetts General Hospital Richard B. Simches Research Center 185 Cambridge Street, MCPZN 7205 Boston, MA 02114 Phone: 617-643-9351
Principal Investigator:	John H. Stone, MD, MPH
Sponsor Protocol No.:	XmAb5871-03
IND No.:	125,319
IMP Name:	XmAb5871
Development Phase:	Phase 2
Version, Date	Version 3.0 Amendment 2, 31 Jan 2017

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: An Open-label, Single-arm, Pilot Study to Evaluate the Effect of XmAb®5871 on Disease Activity in Patients with IgG4-Related Disease

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.

31 Jan 2017
Date

SIGNATURE PAGE

Declaration of the Principal Investigator

Protocol Title: An Open-label, Single-arm, Pilot Study to Evaluate the Effect of XmAb®5871 on Disease Activity in Patients with IgG4-Related Disease

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.

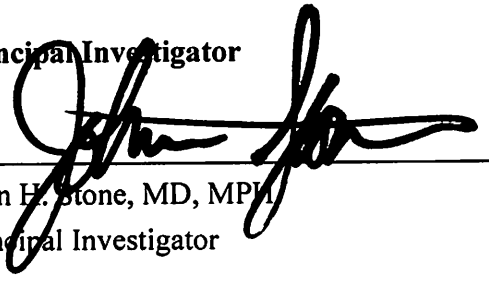
I will provide copies of the protocol and of the clinical and preclinical information on the investigational product, which was furnished to me by the Sponsor, to all members of the study team responsible to me who participate in the study. I will discuss this material with them to assure that they are 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 31 Jan 2017. 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



John H. Stone, MD, MPH
Principal Investigator

2/6/2017
Date

PROTOCOL SYNOPSIS

Protocol Title:	An Open-label, Single-arm Pilot Study to Evaluate the Effect of XmAb®5871 on Disease Activity in Patients with IgG4-Related Disease
Protocol Short Title	XmAb5871 Phase 2 Open-label Multiple-Dose Study in Patients with IgG4-RD
Study Number:	Sponsor Protocol No.: XmAb5871-03
Investigational Product	XmAb5871
IND Number	125,319
Development Phase:	Phase 2
Indication	IgG4-Related Disease (IgG4-RD)
Sponsor:	Xencor, Inc.
Principal Investigator:	John H. Stone, MD, MPH
Study Center(s):	The study will be conducted at the Massachusetts General Hospital (Boston, MA) and up to 2 additional sites.

Study Objectives:	**Primary Objective**
	• To evaluate the effect of every other week intravenous (IV) administration of XmAb5871 on the IgG4-RD Responder Index (RI) in patients with active IgG4-RD
	Secondary Objective
	• To evaluate the safety and tolerability of every other week IV administration of XmAb5871 in patients with active IgG4-RD
	• To evaluate the pharmacokinetics (PK) and immunogenicity of every other week IV administration of XmAb5871 in patients with active IgG4-RD
	Exploratory Objectives
	• To characterize the pharmacodynamics (PD) of every other week IV administration of XmAb5871 in patients with active IgG4-RD as follows:
	  • To evaluate the effect of XmAb5871 on changes in the absolute B cell count (ABC)
	  • To evaluate the effect of XmAb5871 on changes in serum IgG4 and IgE concentrations
	  • To evaluate the effect of XmAb5871 on changes in the circulating plasmablast count, changes in plasmablast markers of apoptosis and changes in plasmablast gene expression
	  • To evaluate the effect of XmAb5871 on changes in ^{18}F FDG PET/CT imaging in patients with active IgG4-RD

Study Design:	This is an open-label, single-arm study of up to 21 patients with active IgG4-RD. Participants will receive XmAb5871 by IV infusion every other week for up to a total of 12 infusions.
Investigational Medicinal Product(s); IMP, Dose and Route of Administration:	XmAb5871 drug product is 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 10.0 (+/- 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 for the first 15 patients, then up to 6 patients treated with either 90 mg fixed dose or 180 mg fixed dose by IV infusion every other week.
Number of Subjects:	Up to 21 patients with active IgG4-RD
Study Population:	Male and female patients with histopathologically proven IgG4-RD with active disease as defined by disease activity in one or more organ systems AND an IgG4-RD RI of ≥3. Patients are not required to have failed prior therapy for their disease to be eligible for this study. Patients with disease in only one organ system whose primary manifestation is fibrosis will be excluded.
Study Duration	After a screening period of up to 28-days, eligible patients will receive XmAb5871 IV every other week for a total of up to 12 doses (22 weeks). Patients will be followed on study for 6 weeks following the last dose for a total study period of up to 32 weeks.
Study Procedures:	After obtaining informed consent, all screening procedures and tests establishing eligibility will be performed within a period of 28 days before dosing. Patients determined to be eligible at screening will return to the study site on study Day 1 at which time baseline procedures and tests will be performed. Following baseline assessments, patients will be administered XmAb5871 as an IV infusion over a 2 hour infusion period at a dose of 5 mg/kg. Patients will be observed for at least 2 hours after the completion of the first administration during which time safety assessments will be performed. All patients will return to the study site on Day 8 for safety, PK and PD assessments. Patients will return on study Days 15, 29, 43, 57, 71, 85, 99, 113, 127, 141 and 155 for XmAb5871 (5 mg/kg) administration over a 1-2 hour infusion period, as well as for safety, PK, PD and disease response assessments. Patients will be required to remain at the study site for observation for at least 1 hour after the completion of each infusion, during which time safety assessments will be performed. All patients completing the treatment period will be followed through at least Day 197/EOS. Safety, PK, PD and disease response assessments will be collected on both Day 169 and Day 197/EOS. Patient participation will be considered complete once EOS study procedures have been 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 stabilization of the AEs/abnormalities. Based on preliminary data in this study showing reduction of IgG4-RD disease activity following treatment with XmAb5871 at 5 mg/kg every 2 weeks and based on data from a previous study in patients with active rheumatoid arthritis suggesting disease response activity at doses as low as 0.3 mg/kg, the study has been amended in this protocol version in order to explore the treatment effect of lower doses of XmAb5871. Following enrollment of the first 15 patients (treated at 5 mg/kg every other week), approximately 3 additional patients will be treated with a fixed dose of 90 mg of XmAb5871 given IV every other week. A second set of up to 3 additional patients may be treated with either 90 mg or 180 mg of XmAb5871. At the discretion of the Investigator and Sponsor, subjects dosed at 90 mg of XmAb5871 may have their dose increased to 180 mg if there has been an inadequate clinical response to therapy. All study procedures will remain the same for these patients except for the administration of a lower dosage of XmAb5871. The dose for the 90 and 180 mg dose subjects will be administered over a 1 hour period at a constant rate.
Criteria for Evaluation:	**Disease Activity:** The following disease activity parameters will be recorded at scheduled intervals throughout the study: • IgG4-RD RI score

	• Physician Global Assessment of Disease Activity (Visual Activity Score) • Patient Global Assessment of Disease Activity (Visual Activity Score) • ^{18}F FDG PET/CT imaging **Safety:** The following safety parameters will be recorded at regular intervals during the study: • Adverse events (CTCAE V4.03) • Physical examinations • 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, IgA, IgG_{1-4}) • B cell and T cell quantification by flow cytometry • Concomitant medications **Immunogenicity:** The following immunogenicity parameter will be recorded during the study: • Anti-XmAb5871 antibodies [anti-drug antibodies (ADA)] **Pharmacokinetics:** Serum XmAb5871 concentration will be measured at pre-dose (trough) and end-of-infusion (peak) for selected infusions. In addition, levels will be obtained on Days 8, 169 and 197/EOS. Peak and trough concentration-time profiles will be compared to biomarker-time profiles to explore the relationship between XmAb5871 serum concentration and biomarker response. Peak and trough concentrations will be evaluated to determine if they differ in patients with different FcγRIIa and FcγRIIb receptor genotypes. **Pharmacodynamics:** • Circulating ABC count • Serum IgG4 • Serum IgE • Circulating plasmablast count • Circulating plasmablast markers of apoptosis • Circulating plasmablast gene expression **Pharmacogenomics:** • FcγRIIa R131H polymorphism • FcγRIIb I232T polymorphism
Statistical Methods:	<u>Sample size considerations:</u> The sample size chosen for this study was based upon precedent set by other pilot studies of similar nature and was not based on power calculations. The sample size is based primarily on feasibility and the desire to gain disease response information and safety information to support further clinical studies. A total of approximately 15 patients are considered suitable to achieve the study objectives. <u>Data Presentation/Descriptive Statistics:</u> Since this is an open label, single-arm clinical trial, descriptive 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. Time-to-event variables (if any) will be summarized by Kaplan-Meier medians and Kaplan-Meier plots. Data listings will be created to support each table and to present all data. The data will be tabulated with respect to patient enrollment, subject disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, efficacy, and safety measures. The efficacy and safety analysis will be performed on the ITT/Safety Population, defined as all patients who received any amount of XmAb5871. PK and PD data will also be displayed graphically, as appropriate. Any deviations from the planned analyses will be described and justified in the final integrated clinical study report.

LIST OF STUDY STAFF

Sponsor:	Xencor, Inc.
Medical Monitor	Debra Zack, MD, PhD 12770 High Bluff Dr., Suite 260 San Diego, CA 92130 Telephone number: 858-480-3893 Email: dzack@xencor.com
Adverse Event Reporting:	Vigilare International 150 N. Radnor Chester Road Suite F200 Radnor, PA 19087 Telephone number: 610-977-0899 Email: angela.pitwood@vigilareintl.com
Contract Research Organization:	The Translational Medicine Group Massachusetts General Hospital Richard B. Simches Research Center 185 Cambridge Street, MCPZN 7205 Boston, MA 02114 Telephone number: 617-643-9351
Principal Investigator:	John H. Stone, MD, MPH Massachusetts General Hospital Rheumatology Associates, Yawkey 2 55 Fruit St. Boston, MA 02114 Telephone number: 617-643-5385 (OFFICE) Email: JHSTONE@mgh.harvard.edu
Clinical Laboratories:	Massachusetts General Hospital (clinical chemistry, hematology, coagulation, urinalysis, pregnancy tests, IgG, IgG_{1-4}, IgM, IgE, IgA, screening absolute B cell count when indicated, hepatitis and HIV serologies): MGH Pathology Core Laboratory 55 Fruit Street Boston, MA 02114, USA Telephone number: 617-724-5227
Clinical Site:	Massachusetts General Hospital Clinical Research Center 55 Fruit Street Boston, MA 02114, USA Telephone number: 617-726-3294
Bioanalytical Laboratory (PK):	Cynthia Wydysh ICON Laboratory Services, Inc. 8282 Halsey Road Whitesboro, NY 13492 Telephone number: 315-768-2527 Fax number: 315-736-2460 Email: Cynthia.Wydysh@iconplc.com

Genotyping Laboratory:	Ryan Newman Cancer Genetics, Inc. 133 Southcenter Court, Suite 400 Morrisville, NC 27560 Telephone number: 919-653-5532 Fax number: 919-653-5542 Email: Ryan.Newman@cgix.com
Immunogenicity (ADA) Assessment Laboratory:	Mallika Kopalle ICON Laboratory Services, Inc. 8282 Halsey Road Whitesboro, NY 13492 Telephone number: 315-768-2834 Email: Mallika.Kopalle@iconplc.com
Mechanistic Studies Laboratory:	Shiv Pillai, MD, PhD Ragon Institute of MGH, MIT and Harvard 400 Tech Square Cambridge MA 02139 Telephone number: 857-268-7005 Email: pillai@helix.mgh.harvard.edu
^{18}F FDG PET/CT Imaging Assessment Laboratory:	Dushyant Sahani, MD Massachusetts General Hospital Department of Radiology 55 Fruit Street Boston, MA 02114, USA Telephone number: 617-726-8396 Fax number: 617-726-4891 Email: dsahani@partners.org
Flow Cytometry B Cell 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
ABC	Absolute B cell count
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
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
DP	Drug product
ECG	Electrocardiogram
EOI	End of infusion
EOS	End-of-study
Fc	Fragment, crystalizable
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
HIV	Human immunodeficiency 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
LDH	Lactate dehydrogenase
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

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
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

PROTOCOL NO. XmAb5871-03

AMENDMENT 2 - 31 JANUARY 2017

"An Open-label, Single-arm, Pilot Study to Evaluate the Effect of XmAb®5871 on Disease Activity in Patients with IgG4-Related Disease"

SUMMARY OF CHANGES – VERSION 2 TO VERSION 3

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:** ~~*15*~~***21***	• Add up to 6 additional patients to be treated in the current protocol
5	Protocol Synopsis (Administration)	**Added the following bolded text:** *Dose and route of administration: Every other week administration of XmAb5871 at 5.0 mg/kg by IV infusion over 1-2 hours* ***for the first 15 patients, then up to 6 patients treated with either 90 mg fixed dose or 180 mg fixed dose by IV infusion every other week.***	• Allow up to 6 additional patients to be treated with one of two fixed doses of XmAb5871 at dosages lower than 5.0 mg/kg used in the first 15 patients
5	Protocol Synopsis (Number of Subjects)	**Changed the following stricken text and added the following bold text:** ~~*15*~~***21***	• Add up to 6 additional patients to be treated in the current protocol
5	Protocol Synopsis (Study Duration)	**Added the following bolded text:** *Patients will be followed* ***on study*** *for 6 weeks following the last dose for a total study period of up to 32 weeks.*	• Clarification of follow-up period while on study
5	Protocol Synopsis (Study Procedures)	**Added the following bolded text:** ***Based on preliminary data in this study showing reduction of IgG4-RD disease activity following treatment with XmAb5871 at 5 mg/kg every 2 weeks and based on data from a previous study in patients with active rheumatoid arthritis suggesting activity at doses as low as 0.3 mg/kg, the study has been amended in this protocol version in order to explore the treatment effect of lower doses of XmAb5871. Following enrollment of the first 15 patients (treated at 5 mg/kg every other week), approximately 3 additional patients will be treated***	• Addition of 6 patients to be treated with one of two fixed doses of XmAb5871 at dosages lower than 5.0 mg/kg used in the first 15 patients

Page	Section	Change (bolded text added; strikethrough text deleted)	Justification
		with a fixed dose of 90 mg of XmAb5871 given IV every other week. A second set of up to 3 additional patients may be treated with either 90 mg or 180 mg of XmAb5871. At the discretion of the Investigator and Sponsor, subjects dosed at 90 mg of XmAb5871 may have their dose increased to 180 mg if there has been an inadequate clinical response to therapy. All study procedures will remain the same for these patients except for the administration of a lower dosage of XmAb5871. The dose for the 90 and 180 mg subjects will be administered over a 1 hour period at a constant rate.	
31	1.3.2.A Randomized, Placebo-controlled double-blinded ascending multiple-dose study of the safety, tolerability, pharmacokinetics and pharmacodynamics of XmAb5871 in patients with rheumatoid arthritis	**Added the following bolded text:** ***In Part A of the study, all cohorts treated with XmAb5871 at any dose tested (0.3, 1.0, 3.0, or 10.0 mg/kg) achieved higher percentages of DAS-CRP low disease or remission at Day 85 than did the placebo-treated patients. For example, in the 0.3 mg/kg group (n=3), there were 33% DAS28-CRP remissions, 100% ACR20, 33% ACR50 and 33% ACR70 responses vs 14%, 29%, 14% and 0% in the placebo group (Part A).***	• Justifying the use of lower dosages
39	3.1 Overall Study Design and Plan	**Changed the following stricken text and added the following bold text:** ***The first 15 patients enrolled*** ~~*All patients*~~ *will receive 5.0 mg/kg of XmAb5871 infused IV over 1-2 hours on an every other week dosing schedule for up to a total of 12 doses.* ***Up to six additional patients may be enrolled and treated with either 90 mg fixed dose or 180 mg fixed dose by IV infusion every other week.*** *Patients will be followed for 6 weeks after the final infusion. Up to* ~~*15*~~***21*** *patients will be enrolled.*	• Adjusting language to add up to 6 patients at one or two fixed dosages lower than 5 mg/kg

Page	Section	Change (bolded text added; strikethrough text deleted)	Justification
40	3.1 Overall Study Design and Plan	**Added the following bolded text:** ***Based on preliminary data in this study showing reduction of IgG4-RD disease activity following treatment with XmAb5871 at 5 mg/kg every 2 weeks and based on data from a previous study in patients with active rheumatoid arthritis suggesting activity at doses as low as 0.3 mg/kg, the study has been amended in this protocol version in order to explore the treatment effect of lower doses of XmAb5871. Following enrollment of the first 15 patients (treated at 5 mg/kg every other week), approximately 3 additional patients will be treated with a fixed dose of 90 mg of XmAb5871 given IV every other week. A second set of up to 3 additional patients may be treated with either 90 mg or 180 mg of XmAb5871. At the discretion of the Investigator and Sponsor, subjects dosed at 90 mg of XmAb5871 may have their dose increased to 180 mg if there has been an inadequate clinical response to therapy All study procedures will remain the same for these patients except for the administration of a lower dosage of XmAb5871. The dose for the 90 and 180 mg dose subjects will be administered over a 1 hour period at a constant rate.***	• Adjusting language to add up to 6 patients at one or two fixed dosages lower than 5 mg/kg
42	3.3 Selection of Patient Population	**Changed the following stricken text and added the following bold text:** ~~*15*~~***21***	• Add up to 6 additional patients to be treated in the current protocol
45	4.1 Number of Patients	**Changed the following stricken text and added the following bold text:** ~~*15*~~***21***	• Add up to 6 additional patients to be treated in the current protocol
49	5.2 Drug Storage and Handling Requirements	**Changed the following stricken text and added the following bold text:** ***For the first 15 patients****, the full calculated dose*	• Clarification of dose
50	5.2 Drug Storage and Handling Requirements	**Added the following bolded text:** ***After the first 15 patients, the next up to 6 patients will be dosed with fixed doses of either 90 mg or 180 mg per dose. The XmAb5871 will be diluted as for the 5.0 mg/kg dose, but instead of weight-based***	• Adjusting language to add up to 6 patients at one or two fixed dosages lower than 5 mg/kg

Page	Section	Change (bolded text added; strikethrough text deleted)	Justification
		dosing, either 18 mL or 36 mL of the solution will be given as a fixed dose.	
51	5.4 Dose Rationale	**Added the following bolded text:** ***This protocol has been amended in order to explore the treatment effect of lower doses of XmAb5871. After the first 15 patients are enrolled, approximately 3 additional patients will be treated with a fixed dose of 90 mg of XmAb5871 given IV every other week instead of 5 mg/kg. A second set of up to 3 additional patients may be treated with either 90 mg or 180 mg XmAb5871 instead of 5 mg/kg. These two doses represent approximately 1 mg/kg and 2 mg/kg for a 75 kg person and are well within the ranges previously studied.***	• Adjusting language to add up to 6 patients at one or two fixed dosages lower than 5 mg/kg
77	7.1.3 End-of-Study	**Added the following bolded text:** ***In addition, the PI and/or study site will contact all patients approximately every 6 months following EOS and will keep a log of when (if) the patient has recurrent symptoms and when (if) new medications for IgG4-RD treatment have been added since the end of study. This information will be provided to the sponsor periodically following the completion of the study.***	• Adding off-study followup
79	8.3 Determination of Sample Size	**Changed the following stricken text and added the following bold text:** ~~*15*~~***21***	• Add up to 6 additional patients to be treated in the current protocol

1 INTRODUCTION

1.1 Background

1.1.1 Role of B Cells in Autoimmunity

Autoimmune diseases, including connective tissue diseases and bullous diseases, 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 erythematosus (SLE) (belimumab). In IgG4-related disease (IgG4-RD), an open-label pilot study has also shown evidence of an effect on disease activity with B cell depletion therapy (Carruthers et al., 2015).

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 the 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, Taransenko 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 IgG4-RD, SLE and RA.

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 the 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 in classical animal models of autoimmune disease.

1.1.3 IgG4-Related Disease

IgG4-RD is a chronic fibro-inflammatory condition that can affect a variety of organs including the pancreas, biliary tract, salivary and lacrimal glands, orbits, lungs, kidneys, meninges, pituitary gland, prostate and thyroid among others. It may also involve the retroperitoneum. This multi-organ immune-mediated condition was previously regarded as a group of isolated single organ diseases but has recently been recognized as a unifying entity linked by common histopathological and immunohistochemical features. The histopathological features include a dense lymphoplasmacytic infiltrate consisting of T cells and IgG4+ plasma cells, storiform fibrosis and obliterative phlebitis. Immunoperoxidase staining of affected tissues generally demonstrate a ratio of ≥40% IgG4/IgG+ plasma cells (Deshpande et al. 2012). Serum IgG4 concentrations are elevated in at least 50-60% of cases before the initiation of treatment (Wallace et al. 2015).

Several B cell subsets have recently been described by flow cytometry to be elevated in the peripheral blood of IgG4-RD patients. Circulating $IgG4^+$ plasmablasts ($CD19^{low}CD38^+CD20^-CD27^+$) have been shown to be elevated in active disease as compared to individuals with other diseases and normal controls, even in IgG4-RD patients with normal IgG4 serum levels. Total plasmablasts can be utilized both as a diagnostic feature of IgG4-RD as well as a biomarker of treatment response (Wallace et al. 2014, Mattoo et al. 2014). CD4+ T cells have been putatively implicated in the pathogenesis of IgG4-RD as well, but the precise type(s) and function(s) of this population have yet to be clarified (Kamisawa et al. 2014).

The frequency of IgG4-RD is unknown in most countries other than Japan, where it is thought to affect at least 8000 individuals (Uchida et al. 2012). However, because this disease has only been recognized and described in the last 10 years, recognition of the disease is growing in other parts of the world, including the US and Europe. IgG4-RD appears to have a modest predilection for affecting men more often than women, and tends to afflict middle-aged to elderly individuals. Although IgG4-RD can affect a single organ at presentation, it is not uncommon for patients to present with or develop multi-organ disease. As the disease progresses, additional organs develop lesions and the cellular inflammation characterizing early disease moves toward a more fibrotic stage, causing major tissue damage, dysfunction and ultimately organ failure.

1.1.4 Current Treatment of IgG4-RD

IgG4-RD is currently incurable. The goals of treatment are to reduce inflammation and swelling in the organs, prevent or reverse (if possible) fibrosis and increase glandular secretion. Aggressive treatment is warranted to prevent organ failure when vital organs are involved. For example, cholangitis due to IgG4-RD can lead to hepatic failure, IgG4-related (type 2) autoimmune pancreatitis can lead to failure of either or both the endocrine and exocrine pancreas, and IgG4-related aortitis can lead to aneurysms and/or aortic dissection. At the present time, glucocorticosteroids at daily doses of 0.6 mg/kg daily for 2 to 4 weeks followed by tapering to low doses (or discontinuing altogether) over 3-6 months is the first line of therapy. Although this approach is effective initially in most patients, the relapse rate upon tapering or discontinuation is high (Khosroshahi et al. 2015). In addition, the long term use of glucocorticosteroids in older populations such as that affected by IgG4-RD can lead to many untoward side effects such as osteoporosis, high blood pressure and diabetes. Immunosuppressive medications such as azathioprine, mycophenolate mofetil and methotrexate have been used as glucocorticosteroid-sparing agents, with no clear indication of efficacy (Stone et al. 2012, Yamamoto et al. 2014, Khosroshahi et al. 2015). A high disease response rate has been observed in one small open-label trial with rituximab, utilizing an IgG4-RD Responder Index (RI) as a measure of disease response (Khosroshahi et al. 2010, Carruthers et al. 2015). The presumed role of B cells and plasmablasts in IgG4-RD and the preliminary observation of an effect on IgG4-RD disease activity by B cell depletion therapy support the evaluation of other non-depleting B cell directed therapies such as XmAb5871.

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 the CD19 of the relevant toxicology species, the cynomolgus monkey, is approximately 6 fold lower than the affinity for the human CD19. No appreciable XmAb5871 binding has been detected with B cells from the mouse, rat, rabbit, or dog.

The second functional attribute important for the pharmacology of XmAb5871 is its 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 the 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 improve FcγRIIb 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 humans and cynomolgus monkeys 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 the cynomolgus monkey.

The co-engagement of CD19 and FcγRIIb is the presumed mechanism by which excess antigen-antibody complexes down regulate B cell activity. XmAb5871 also binds these 2 receptors simultaneously, thereby inhibiting B cell activation. 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 binding to 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 downregulating B cell activity, even if such antibodies were used in combination.

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, the 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 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

The binding affinity of XmAb5871 for FcγRIIb is increased approximately 225-fold compared to native human IgG1 Fc. Moreover, its binding affinity to the activating receptor FcγRIIIa, involved in antibody-dependent cell-mediated cytotoxicity (ADCC) by NK cells, is reduced approximately 20-fold compared to the same 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. In contrast, two 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 the antibody-dependent cell-mediated phagocytosis (ADCP) function of macrophages. Two alleles of the gene encoding FcγRIIa generate 2 variants that differ at amino acid position 131. The histidine (H131) and arginine (R131) alleles are distributed roughly equally in humans, 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. The potential implications of this increased binding to FcγRIIa R131 (i.e., ADCP) have been examined. In vitro phagocytosis experiments demonstrate that monocyte-derived macrophages from R131 positive donors phagocytose Ramos cells ($CD19^+$ B cell line) and purified human B cells in the presence of XmAb5871. Very little phagocytosis was observed with monocyte-derived macrophages from H131 homozygous donors. These observations raise the possibility of B cell reduction or depletion in R131-positive patients. However, data from the first-in-human (FIH) study in healthy volunteers as well as data from the multiple ascending dose study in RA patients, both described below, have not shown an association 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 the 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 that lacks 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 activate platelets fully for secretion and aggregation. The potential for platelet interaction was evaluated even though neither CD19 nor FcγRIIb are platelet-associated antigens. In an ex vivo study, the addition of XmAb5871 to samples from human donors did not induce platelet activation. Moreover, 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, no signs or symptoms consistent with either cytokine release syndrome or immunologically-mediated infusion-related reactions were observed. In the Phase 2a study in RA patients, two of 40 XmAb5871-treated patients (5%) experienced an infusion-related reaction with hypotension, both at a dose of 10 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 the binding of XmAb5871 to lymphocytes in flow cytometric analyses. 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 the FcγRIIb of the cynomolgus monkey was approximately 250-fold lower 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 that 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 that 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 in that study, 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 monkey of both genders. XmAb5871 was administered via 1 hour IV infusion at doses of 0, 2, 10 or 50 mg/kg on an every other week x 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-related 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.

Anti-drug antibodies (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 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, or 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 monkey following IV infusions of up to 200 mg/kg XmAb5871 every 14 days for up to 6 months. These studies 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 XmAb5871 in Healthy Adult Volunteers

In the FIH study, 48 healthy male subjects were enrolled and were randomized 3:1 (XmAb5871:placebo) in a double-blind manner to receive a single IV infusion of XmAb5871 or matching placebo administered over a 2 hour period. Thirty-six subjects received single IV infusions of XmAb5871 at dose levels of 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). Twelve subjects received placebo. All completed the study.

XmAb5871 was generally 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 patients who experienced TEAEs in the active treatment groups 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 (38.9%) XmAb5871 subjects, 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 XmAb5871 cohort who reported nausea of severe intensity. Eight subjects (22%) had their XmAb5871 IV infusion temporarily interrupted as a result of the infusion-related gastrointestinal symptoms. These temporary suspensions occurred at doses of 0.2 to 10.0 mg/kg. 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 monophasically. Clearance decreased with increasing dose approaching a constant value at the higher dose levels (0.6-10.0 mg/kg). The volume of distribution decreased with dose increment approaching a value that was similar to physiologic serum volume. The 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 recovery.

Sixteen of 36 (44%) XmAb5871-treated subjects had at least one sample positive for ADA. Distinct evidence of ADA-mediated clearance of XmAb5871 occurred in only one ADA-positive subject (in the 5 mg/kg cohort) 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 cells followed XmAb5871 administration. The nadir mean CD20+ B cell count, approximately 40% to 50% of baseline cell counts, occurred roughly between Day 4 and Day 8. The degree of CD20+ B cell count reduction did not increase significantly as the dose of XmAb5871 increased. The recovery of the B cell count approximated the observed kinetics of XmAb5871 clearance. No association between the presence of the FcγRIIa R131 polymorphic allele and the CD20+ B cell count at nadir was observed.

The expression of CD86 on B cells is 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 XmAb5871 in Patients with Rheumatoid Arthritis

A multiple ascending 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 despite the use of disease modifying anti-rheumatic agents (DMARDS). 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 (double-blind) 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), administered up to 6 times at 2-week intervals.

A total of 57 RA patients were enrolled in the study, 30 in Part A and 27 in Part B. One patient 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 3 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 TEAEs (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 in general 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 two 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 of study drug, 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 roughly monophasically over time. The C_{max} for the first and last dose increased in a manner slightly greater than proportional to the dose. The AUC for the first and last dose increased proportionally to the dose increment. At the dose levels studied, neither clearance nor volume of distribution showed any significant dependence on dose following either the first or last administration. There was little accumulation between the first and last doses with the 2-week dosing interval.

Across all 4 dose levels, last dose clearance averaged 15.16 ± 3.68 mL/day/kg. The last dose volume of distribution averaged 49.27 ± 14.17 mL/kg. This figure is close to the literature value for physiological serum volume. The 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. The peripheral B cell count decreased in all cohorts following the first dose, with cohort mean levels in the range of 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 occurred 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., most 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 ADA at the time of second infusion with increasing titer ADA thereafter. 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, only 12.5% (1/8) and 0% (0/8) of the placebo treated patients achieved ACR50 and ACR70 responses, respectively.

In Part A of the study, all cohorts treated with XmAb5871 at any dose tested (0.3, 1.0, 3.0, or 10.0 mg/kg) achieved higher percentages of DAS-CRP low disease or remission at Day 85 than did the placebo-treated patients. For example, in the 0.3 mg/kg group (n=3), there were 33% DAS28-CRP remissions, 100% ACR20, 33% ACR50 and 33% ACR70 responses vs 14%, 29%, 14% and 0% in the placebo group (Part A).

Data collected during the Phase 2a study confirms that XmAb5871 binds as intended to the circulating B cell CD19 receptor and a beneficial trend towards reducing RA disease activity was observed.

The Sponsor will immediately notify the Principal Investigator 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

The presumed role of B cells and plasmablasts in IgG4-RD and the preliminary observation of an effect on IgG4-RD disease activity by B cell depletion therapy support the evaluation of non-depleting B cell-directed therapies such as XmAb5871. 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 IgG4-RD. 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 studies completed in humans. 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, however, suggesting that the toxicology species is informative.

The observed reduction in absolute B cell count (ABC) 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. Even the complete absence of detectable circulating B cells is regarded as a manageable safety risk in humans. 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. Two subjects in the multiple dose Phase 2a study, 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 an ADA response with titers that increased over time. 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 antibody therapies, 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 assessed continuously 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 end of the first infusion.

The frequency of vital sign monitoring will be modified slightly 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 patients

(over the dose range 0.2 mg/kg to 10.0 mg/kg) had their XmAb5871 IV infusion interrupted temporarily because of the self-limited gastrointestinal-related symptoms of short duration (abdominal discomfort, abdominal pain, epigastric discomfort, nausea and vomiting). In all cases, the patients 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, reversible reductions in B cell levels were observed in the two repeat-dose GLP toxicology studies performed to date. In both the 12-week (six 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 two 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).

In both clinical studies performed to date, reversible reductions in ABCs were observed. The ABCs declined to 50-60% of baseline levels, with 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. Prolonged reductions in B cell counts to the extent seen with B cell depleting therapies have not been observed and are not expected with XmAb5971. B cell depleting therapies have been widely used both in hematologic malignancies and in autoimmune diseases. 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 effect of XmAb5871 on the disease activity of IgG4-RD. Based on the effect of XmAb5871 on B cell function observed in in vitro, in vivo, and clinical studies and on the trends in improvement in RA disease activity observed, some IgG4-RD patients may experience improvement in disease activity.

1.4.4 Conclusion

XmAb5871 is being developed for the treatment of autoimmune disease including IgG4-RD. An open-label pilot trial to evaluate effects on disease activity is proposed. Given the established role of B cells in the pathogenesis of IgG4-RD and the effects of XmAb5871 on B cell function, XmAb5871 may provide an attractive therapeutic option for this condition. There is presently no FDA-approved therapy for the treatment of IgG4-RD.

The design of the proposed trial contains measures appropriate to the mitigation of risk factors for adverse events. Furthermore, 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 evaluate the effect of every other week intravenous (IV) administration of XmAb5871 on the IgG4-RD Responder Index (RI) in patients with active IgG4-RD

2.2 Secondary Objective

- To evaluate the safety and tolerability of every other week IV administration of XmAb5871 in patients with active IgG4-RD
- To evaluate the pharmacokinetics (PK) and immunogenicity of every other week IV administration of XmAb5871 in patients with active IgG4-RD

2.3 Exploratory Objectives

- To characterize the pharmacodynamics (PD) of every other week IV administration of XmAb5871 in patients with active IgG4-RD, as follows:
  - To evaluate the effect of XmAb5871 on changes in the absolute B cell count (ABC)
  - To evaluate the effect of XmAb5871 on changes in serum IgG4 and IgE concentration
  - To evaluate the effect of XmAb5871 on changes in the circulating plasmablast count, changes in plasmablast markers of apoptosis, and changes in plasmablast gene expression
  - To evaluate the effect of XmAb5871 on changes in ^{18}F FDG PET/CT imaging in patients with active IgG4-RD

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is an open-label, single-arm, multiple-dose study to investigate the effect of XmAb5871 on disease activity, safety, tolerability, PK, immunogenicity and PD of XmAb5871 in patients with active IgG4-RD. The study will be conducted in centers with expertise in this disease.

The first 15 patients enrolled will receive 5.0 mg/kg of XmAb5871 infused IV over 1-2 hours on an every other week dosing schedule for up to a total of 12 doses. Up to six additional patients

may be enrolled and treated with either 90 mg fixed dose or 180 mg fixed dose by IV infusion every other week. Patients will be followed for 6 weeks after the final infusion. Up to 21 patients will be enrolled.

After obtaining informed consent, all screening procedures and tests establishing eligibility will be performed within a period of 28 days before dosing. Patients determined to be eligible at screening will return to the study site on Day 1, at which time baseline procedures such as physical examination and the collection of blood and urine samples will be performed. Eligible patients will be administered XmAb5871 as an IV infusion over a 2 hour infusion period at a dose of 5 mg/kg. Patients will be observed for at least 2 hours after the first administration, during which time safety assessments will be performed.

All patients will return to the study site on Day 8 for safety, PK and PD assessments. Patients will return on study Days 15, 29, 43, 57, 71, 85, 99, 113, 127, 141 and 155 for XmAb5871 (5 mg/kg) administration over a 1-2 hour infusion period and for safety, PK and PD assessments as outlined in Table 6: Schedule of Assessments. Patients will be required to remain at the study site for observation for at least 1 hour after the completion of each infusion. Post-treatment visits for safety, PK and PD will occur on Days 169 and 197/EOS.

Based on preliminary data in this study showing reduction of IgG4-RD disease activity following treatment with XmAb5871 at 5 mg/kg every 2 weeks and based on data from a previous study in patients with active rheumatoid arthritis suggesting activity at doses as low as 0.3 mg/kg, the study has been amended in this protocol version in order to explore the treatment effect of lower doses of XmAb5871. Following enrollment of the first 15 patients (treated at 5 mg/kg every other week), approximately 3 additional patients will be treated with a fixed dose of 90 mg of XmAb5871 given IV every other week. A second set of up to 3 additional patients may be treated with either 90 mg or 180 mg of XmAb5871. At the discretion of the Investigator and Sponsor, subjects dosed at 90 mg of XmAb5871 may have their dose increased to 180 mg if there has been an inadequate clinical response to therapy. All study procedures will remain the same for these patients except for the administration of a lower dosage of XmAb5871. The dose for the 90 and 180 mg dose subjects will be administered over a 1 hour period at a constant rate.All patients completing the treatment period will be followed through at least D197/EOS (or for 6 weeks following the last infusion for early termination). Patient participation is complete once EOS study procedures are performed.

Signs and symptoms of IgG4-RD disease activity will be measured periodically throughout the study using a modification of the IgG4-RD RI (Carruthers et al. 2012). The IgG4-RD RI is

based on the Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (Stone et al. 2001) utilized for the evaluation and licensure of rituximab in ANCA-associated vasculitis (Stone et al. 2010). The IgG4-RD RI is an instrument designed to detect change in disease activity and identify improvements and worsening in the same or different organ systems and has been used in a prior clinical trial to monitor IgG4-RD disease activity (Khosroshahi et al. 2010, Carruthers et al. 2015). ^{18}FDG PET/CT imaging, which has been reported to have disease activity monitoring utility in IgG4-RD (Matsubayashi et al. 2009), will be obtained at baseline and after 3 and 6 months of therapy as an exploratory measure of disease activity.

All AEs, including serious AEs and deaths and information about concomitant medication use, 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 such abnormalities have resolved or stabilized.

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 IgG and IgE, by enumeration of circulating B cells and plasmablasts, and by evaluation of markers of plasmablast apoptosis and gene expression.

In addition, FcγRIIa and FcγRIIb genotypes will be determined.

Patients may also consent to optional predose and/or postdose biopsy of involved tissue(s).

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 this study, all patients will receive the active investigational medicinal product XmAb5871. Because this is an open-label pilot Phase 2 study to investigate the effect of XmAb5871 on IgG4-RD disease activity, an appropriate sample size cannot be determined on a statistical basis, owing to the absence of adequate information to perform formal sample size calculations. The sample size has been selected to provide information on safety, tolerability, PK, efficacy and PD following multiple doses of XmAb5871. The study is designed to obtain preliminary information on the effect of XmAb5871 on IgG4-RD disease activity and safety of XmAb5871 in IgG4-RD before the initiation of a randomized, double blind placebo controlled study in this disease.

3.3 Selection of Patient Population

Up to 21 evaluable patients will be enrolled in the study. The sample size chosen for this study was based upon precedent set by other pilot studies of similar nature and was not based on power calculations. The sample size is based primarily on feasibility and the desire to gain efficacy and safety information to support the design of randomized, placebo-controlled trials.

3.4 Endpoints

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

3.4.1 Disease Activity

Primary outcome measure will be the proportion of patients on Day 169 with an improvement of disease activity as defined by a decrease of IgG4-RD RI $\geq$ 2 points from Day 1 pre-dose disease activity score.

In addition, the proportion of patients with 1) a decline of the IgG4-RD RI of $\geq$ 2 points compared to baseline (Day 1), 2) no disease flares during the study, and 3) no glucocorticoid use between months 2 and 6 will be determined. Disease flare is defined as increase in the IgG4-RD RI of $\geq$ 2 and/or the need for increase in steroids or institution of additional therapy for IgG4-RD.

The proportion of patients with disease improvement at any time and the duration and the degree of improvement in IgG4-RD RI will also be examined.

The following disease parameters will be measured:

- IgG4-RD Responder Index (RI)
- Physician Global Assessment of Disease Activity (Visual Activity Score)
- Patient Global Assessment of Disease Activity (Visual Activity Score)
- ^{18}F FDG PET/CT imaging

3.4.2 Mechanistic Studies

Blood will be collected for mechanistic studies at pre-dose baseline and at multiple time points during the treatment and follow-up phases. These studies may include the following: enumeration of plasmablast levels; quantification of levels of B cell activation markers on B

cells; total multi-parametric peripheral blood white cell population analysis by Cytof mass cytometry (at the Ragon Institute); analysis of plasmablasts for markers of apoptosis and activation by flow cytometry and by RNA-seq before and after therapy. The results from these studies may be reported separately from the clinical study report.

3.4.3 Safety Endpoints

Secondary outcome measures will include patient incidence of TEAEs and clinically significant changes in safety laboratory tests, physical examination findings, vital signs, and ECGs.

Safety and tolerability will be assessed with the following:

- Adverse event assessments
- 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 siting position
- 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
- Physical examinations
- Serum immunoglobulin (Ig) levels (IgG, IgM, IgE, IgA, IgG_{1-4})
- Complement levels C3 and C4
- Monitoring for pregnancy in women of child-bearing age only

3.4.4 Immunogenicity Endpoint

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

3.4.5 Pharmacokinetic Endpoints

Pre-dose (trough) and end-of-infusion (peak) XmAb5871 serum concentrations will be measured on selected study days. 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)
- Serum IgG4 and IgE concentration
- Number of circulating plasmablasts
- Markers of plasmablast apoptosis and gene expression

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 patient in the study in the interest of 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.

Enrollment will be suspended if ANY of the criteria listed below are met. If the study is suspended due to meeting any of the criteria below, it may only be restarted after review and agreement by the PI and Sponsor.

- The occurrence of 2 or more SAEs that are assessed as drug-related
- The occurrence of a severe AE, assessed as related to the study drug, of similar origin in 3 or more patients

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 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 subject will be permanently discontinued from the study drug treatment.

There will be no dose level modification in this study.

4 STUDY POPULATION

The study population will consist of male and female patients with histopathologically proven IgG4-RD and activity in one or more organ systems AND with an IgG4-RD RI of ≥3. Patients are not required to have failed prior therapy for their disease to be eligible for this study.

Patients with disease in only one organ system whose primary manifestation is fibrosis will be excluded. Patients must be able to provide written informed consent and meet all the inclusion criteria and none of the exclusion criteria.

4.1 Number of Patients

Up to 21 evaluable patients will be enrolled in the study. The sample size is based on practical considerations and is consistent with the goals of this phase 2 pilot study.

4.2 Inclusion Criteria

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

1. Are male or female between 18 to 80 years of age, inclusive.
2. Have active disease based on an IgG4-RD RI ≥3 and may or may not have received prior IgG4-RD therapy.
3. Have a compatible pattern of organ involvement consistent with IgG4-RD that cannot be attributed to other causes.
4. Have a histopathologically-proven diagnosis of IgG4-RD: at least two out of the three major features of lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis.
5. Have a peripheral blood plasmablast count of > 900 cells/mL and/or an elevated IgG4 level during screening.
6. Are judged by the investigator as likely to be able to discontinue any baseline prednisone within two months of enrollment.

7. History of a negative test result for HIV I and II antibody, hepatitis B surface antigen, hepatitis B core antibody and hepatitis C antibody within 60 days before first dose of XmAb5871.
8. Are able and willing to complete the entire study according to the study schedule.
9. Are willing to forego other forms of experimental treatment during the study.
10. Are able to provide written informed consent.

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, hepatic, metabolic, hematologic or psychiatric) other than IgG4-RD that, in the opinion of the Investigator would pose a risk to patient safety or interfere with the study evaluation, procedures or completion.
2. Malignancy within 5 years (except successfully treated in situ cervical cancer, resected squamous cell or basal cell carcinoma of the skin, or prostate cancer with no recurrence ≥3 years following prostatectomy).
3. Presence of recurrent or chronic infections, defined as ≥3 infections requiring antimicrobials over the past 6 months prior to screening.
4. Active infection requiring hospitalization or treatment with parenteral antimicrobials within the 60 days prior to randomization or oral antimicrobials within the 21 days prior to enrollment.
5. Patient is taking > 40 mg of prednisone QD (or the equivalent, refer to Table 1)
6. Prior use of rituximab (or other B cell depleting agents) within 3 months of enrollment. Prior use of any B cell depleting agent greater than 3 months from enrollment is allowed if circulating plasmablasts are ≥ 900 cells/mL.
7. Use of any investigational agent within 5 half-lives of the agent (or 6 months if the half-life is unknown) prior to enrollment.
8. Immunosuppressive agent use within the three months prior to enrollment (e.g. methotrexate, mycophenolate mofetil, 6-mercaptopurine, tacrolimus, cyclophosphamide or azathioprine).
9. White blood cell count < 2.5 x $10^3/\mu L$.

10. Absolute neutrophil count (ANC) < 1.0 x $10^3/\mu L$.
11. Elevated serum creatinine > 1.5 x ULN, unless the decline in renal function is known to be caused by IgG4-related renal disease in which case serum creatinine must not be >2.0 x ULN.
12. Hemoglobin < 10 g/dL.
13. Platelet count < 75,000 x $10^9/L$.
14. Has received live vaccines within 2 months of enrollment.
15. Inability to communicate reliably with the investigator.
16. Patient is pregnant or breast feeding, or planning to become pregnant while enrolled in the study, up to EOS visit.
17. Positive pregnancy test at screening or during the study.
18. Subjects who do not agree to use medically acceptable methods of contraception (as defined in Section 5.10.2).
19. Male patient with a pregnant partner who is not willing to use a condom during the treatment and up to EOS visit.
20. Known or suspected sensitivity to mammalian cell-derived products or any components of the study drug.
21. History of alcohol and/or substance abuse within 12 months prior to screening.
22. Unable or unwilling to partake in follow-up assessments or required protocol procedures.

4.4 Subject 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 subject withdraws from the study prematurely. All patients who withdraw from the study with an ongoing AE must be followed until the event is resolved or deemed stable. At the time that a patient withdraws prematurely for any reason, all assessments as listed for the Day 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 197/EOS visit should be performed. If a subject withdraws prematurely after dosing, all data to be collected prior to discharge from the clinical site will be collected at the time of premature

discontinuation or at the scheduled end of study visit. Subject 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. Subject withdrew consent
5. Other

A comprehensive effort must be made to determine the reason(s) why a subject fails to return for the necessary visits or is discontinued from the study. If the subject is unreachable by telephone, a registered letter, at the minimum, should be sent to the subject 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 if deemed necessary by the Sponsor. 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 the site closed for whatever 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 (DP) 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: IgG4-RD

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

Dosage form: Solution for infusion

Route of administration: 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 DP must be stored under refrigeration at 2 to 8^{o}C (+/- 5^{o}C). Prior to administration, XmAb5871 DP should be removed from storage temperature conditions and allowed to equilibrate to room temperature. Undiluted XmAb5871 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 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.

For the first 15 patients, 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.

After the first 15 patients, the next up to 6 patients will be dosed with fixed doses of either 90 mg or 180 mg per dose. The XmAb5871 will be diluted as for the 5.0 mg/kg dose, but instead of weight-based dosing, either 18 mL or 36 mL of the solution will be given as a fixed dose.

XmAb5871 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 (DP) should be inspected visually. XmAb5871 DP 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 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 will be performed as described in the Pharmacy Manual, which will be provided to the sites.

Diluted XmAb5871 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 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 should take place as soon as possible following dilution. If a delay is anticipated, diluted XmAb5871 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 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. 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 X 13 infusions) was 200 mg/kg. The dosing schedule and duration of the toxicity study provides support for the dose/schedule of the proposed pilot study. The completed FIH study examined single doses from 0.03 mg/kg, a dose predicted to result in a Cmax about 5-fold below the estimated 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 X 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 trial, a dose of 5 mg/kg has been selected for this study.

This protocol has been amended in order to explore the treatment effect of lower doses of XmAb5871. After the first 15 patients are enrolled, approximately 3 additional patients will be treated with a fixed dose of 90 mg of XmAb5871 given IV every other week instead of 5 mg/kg. A second set of up to 3 additional patients may be treated with either 90 mg or 180 mg XmAb5871 instead of 5 mg/kg. These two doses represent approximately 1 mg/kg and 2 mg/kg for a 75 kg person and are well within the ranges previously studied.

5.5 Supply, Packaging, and Labeling

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

XmAb5871 DP 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.

Each product vial is intended to deliver at least 10 mL of drug solution or 100 mg (+/- 5%) of XmAb5871.

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 Subject Identification

5.7.1 Screening Numbers

All screened patients will be assigned a unique subject identification (SID) number. The SID numbers are consecutive 4-digit numbers that identify patients from time of Screening until time of enrollment (i.e., time at which the patient has been determined to meet all inclusion criteria and no exclusion criteria). Each SID will start with a 9 in the first digit position. The first subject screened will be assigned the SID 9001, the second 9002, the third 9003 etc. Patients who drop out of the clinical study before enrollment will retain their SID number.

5.7.2 Enrollment Numbers

At enrollment, patients will be assigned consecutive 4-digit enrollment numbers. The first subject randomized will be assigned 1001, the second 1002, the third 1003 and so forth.

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 at an elevation of 0 to 90 degrees. 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 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

Disallowed previous or concomitant medications:

- Prior use of rituximab (or other B cell depleting agents) within 3 months of enrollment. Prior use of any B cell depleting agent greater than 3 months from enrollment is allowed if circulating plasmablasts are ≥ 900 cells/mL.
- Use of any investigational agent within 5 half-lives of the agent (or 6 months if the half-life is unknown) prior to enrollment.
- Received live vaccines within 2 months of enrollment.
- Immunosuppressive agents (e.g. methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide, tacrolimus, 6-mercaptopurine) within 3 months of enrollment.
- Patient is taking > 40 mg of prednisone QD (or the equivalent, refer to Table 1)

Table 1: Prednisone Equivalence

Prednisone	40	mg
Hydrocortisone	160	mg
Prednisolone	40	mg
Triamcinolone	32	mg
Methylprednisolone	32	mg
Dexamethasone	6	mg
Betamethasone	4.8	mg
Cortisone acetate	200	mg

Details of all prior and concomitant medication must be recorded at study entry (i.e., at the first visit) including prior treatment for IgG4-RD, prior IgG4-RD 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 must 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. If the change influences the subject'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 subject safety and acceptable standards of medical care the Investigator will be permitted to 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 of childbearing potential must have a negative pregnancy test during screening and at baseline (Day 1) and must use 1 highly effective method of birth control during the study and for 3 months following last dose of XmAb5871. Highly effective methods of birth control include hormonal birth control, intrauterine devices (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.

Women of non-childbearing potential must have 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).

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

6.1.1 Medical History, Demographic, and Other Baseline Information

The medical history comprises:

- General medical history including IgG4-RD 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 (AE) reporting will begin with the signing of the informed consent document (Screening) and will continue until the last study visit.

6.1.2.1 Definitions

An AE is any untoward medical occurrence in a study subject administered an IMP. The AE 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 IMPs, lack of efficacy may be 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.

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 subject'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. AE - Yes

6.1.2.2 Recording of Adverse Events

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

Adverse events may be volunteered spontaneously by the study subject, 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 subject'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 date (and time, if known) that the investigator or study site is first made aware of the AE (or any subsequent follow up information is received) will be documented. 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 (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 subject 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 in Table 3 and all contributing factors.

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 subject in the past is readministered to that subject. 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 at any dose if it:

- Results in death;
- Is life-threatening; this means that the subject 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 subject 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: Definition of Anaphylaxis below).

Table 4: Definition of Anaphylaxis

Anaphylaxis is highly likely when any <u>one</u> 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 <u>likely</u> 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 *<u>known</u> 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 X 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 FIH single-dose 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 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 the 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 subject 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 subject'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 subject 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 subject'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, to which the PI or an authorized delegate must respond to Vigilare within 24 hours of the request.

SERIOUS ADVERSE EVENT REPORTING INSTRUCTIONS

SAEXmAb5871-03@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 subject, 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 subject 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. The Investigator must follow-up and document the course and the outcome of all pregnancies even if the subject 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 and 197. 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 subject 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, 57, 113, 155, and 197. 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 subject 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

Complete physical examinations will be performed at Screening and on Days 1 and 169. Abbreviated, symptom directed PE will be performed on Days 8, 15, 29, 57, 85, 113, 141, and 197 (EOS).

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

6.1.6 Clinical Laboratory Assessments

Safety clinical laboratory assessments will be performed by the Pathology Core Laboratory of the Massachusetts General Hospital, Boston, MA. 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 Gentris, Morrisville, NC. Plasmablast and mechanistic studies will be done at Ragon Institute, Cambridge, MA.

Blood samples should be taken using standard venipuncture techniques. Blood sampling will be performed according to MGH 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, and 197: 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, 15, 29, 57, 85, 113, 141, 169, and 197. Tube 1: total protein, sodium, potassium, calcium, chloride, bicarbonate (HCO_3), albumin, glucose, blood urea nitrogen (BUN), creatinine,

total bilirubin, alkaline phosphatase (AP), aspartate aminotransferase (AST), alanine aminotransferase (ALT). Tube 2: gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), amylase and lipase. Tube 3: uric acid, inorganic phosphate and creatine phosphokinase (CPK).

Immunoglobulin: Serum IgG, IgE, IgM, IgA and IgG_{1-4} will be assessed at Screening and on Days 1, 8, 15, 29, 57, 85, 113, 141, 169, and 197.

Complement levels: C3 and C4 levels will be assessed at Screening and on Days 1, 15, 29, 57, 85, 113, 141, 169, and 197.

Coagulation: The following coagulation parameters will be assessed on Screening, and Days 1, 8, 29, 85, 141, and 197: 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, 85, 141, and 197: pH, glucose, ketones, specific gravity, nitrite, protein, bilirubin, urobilinogen, leukocytes and blood. Microscopic urinalysis will be performed if clinically indicated.

Serology: Anti-HIV Type I and II Ab, HBsAg, HBcAb, and HCV Ab will be performed at Screening.

Urine Pregnancy Test: Urine pregnancy testing will be performed in female patients on the first Screening Day and at Days 1, 71 and 197(EOS).

Serum Pregnancy Test: A stat serum pregnancy test for women of child-bearing age will be obtained and a negative result verified before each of the ^{18}F FDG PET/CT scans (during the screening period immediately prior to the PET/CT scan and on Day 85).

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 at Screening and on Days 1, 29, 71, 99, 155, 169, and 197.

Flow Cytometry B Cell and T Cell Assessment:

For any patients with a history of rituximab or other anti-CD20 therapy, an initial B cell count will be performed during Screening to ensure that the patient's B cell level has returned to normal levels.

For enrolled patients, CD20+ B cells, T cells, and NK cells will be quantified on Days 1, 8, 15, 29, 57, 85, 113, 141, 169, and 197.

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 on Days 1, 8, 15, 29, 57, 85, 113, 141, 169, and 197.

Plasmablast Assessment and Mechanistic Studies:

Plasmablasts will be enumerated at the Screening visit.

For those enrolled in the study, mechanistic studies that will be performed on Days 1, 8, 43, and 85 may include one or more of the following studies: plasmablast population quantification, total multi-parametric PBMC population analysis using Cytof mass cytometry, analysis of markers of plasmablast apoptosis in flow cytometry and RNA-seq experiments before and after IMP therapy. Additional samples will be collected on Days 15, 29, 57, 71, 99, 113, 127, 141, 155, 169, and 197 and stored for potential mechanistic studies.

Blood Requirements:

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

Hematology: Blood (3 mL) will be collected into a lavender-top tube.

Chemistry: Blood (9 mL) will be collected into 3 green-top tubes of 3 mL each.

Serology: Blood (3.5 mL) will be collected into a gold-top tube.

Serum pregnancy (3 mL) will be collected into a lavender-top tube.

Follicle Stimulating Hormone: Blood (3 mL) will be collected into a lavender-top tube.

Coagulation panel: Blood (5 mL) will be collected into a blue top tube.

Immunoglobulins (IgG, IgM, IgA, IgE, IgG_{1-4}): Blood (5 mL) will be collected into a serum gel (STT) tube.

Complement C3 and C4: Blood (5 mL) will be collected in a gold-top tube on ice.

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 (see Section 6.4 below).

Flow Cytometry B Cell and T Cell Assessment, CD19 RO: Blood (3 mL) will be collected into a lavender-top tube and blood (5 mL) will be collected in a Cyto-Chex BCT glass streck CE marked tube.

Plasmablast Assessment and Mechanistic Studies: Blood (25.5 mL) will be collected into 3 yellow-top ACD tubes.

The total blood volume collected for clinical labs (including PK samples) over the duration of the study will be approximately 920 mL collected on 16 different days with volumes ranging from 33.5 to 89 mL at time of blood draw. Women of child-bearing potential will have an additional 6 mL drawn for pre-PET scan stat serum pregnancy tests.

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 IMP dosing: prior to the start of the infusion and at EOI on Study Days 1, 15, 29, 43, 71, 99, 127, and 155 and at visit time on Days 8, 169 and 197. 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. The PK parameters listed in Section 3.4.4 will be calculated from the serum concentration-actual time profiles.

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, number of circulating IgG4+ plasmablasts and total plasmablasts, and serum IgG4 and IgE concentrations.

6.4 Pharmacogenomics Variables

Blood will be collected as outlined as in Table 6: Schedule of Assessments, on Day 1 (pre-dose) 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.

6.4.1 Efficacy Measurements

The following efficacy assessments will be performed according to the time points defined in Table 6: Schedule of Assessments.

6.4.1.1 IgG4-RD Responder Index

Disease activity will be measured at Screening and on Days 1, 15, 29, 57, 85, 113, 141, 169, and 197 (EOS). For determination of the IgG4-RD responder index as described in the schedules of assessments (IgG4-RD RI), the following criteria will be used (modified after Carruthers et al. 2012):

Organ site, symptomatic, urgent disease (as per IgG4-RD RI) over the previous 28 days

The original IgG4-RD RI has been modified to include the full spectrum of organs affected most frequently by IgG4-RD and to eliminate serum IgG4 concentrations as part of the instrument. In addition, an assessment of damage caused by IgG4-RD in each affected organ is included. A sample assessment form is included in Appendix 11.1.1.

6.4.1.2 Disease Activity VAS

The physician's and patient's overall assessment of the patient's current disease activity will be recorded on a 100 mm linear horizontal VAS, where the left hand extreme of the line is considered "non" (symptom free and no IgG4-RD symptoms) and the right hand extreme is considered "maximum" (maximum IgG4-RD activity). Assessments will be performed at Screening and on Days 1, 15, 29, 57, 85, 113, 141, 169, and 197 (EOS).

Details on the efficacy assessments can be found in Appendix 11.1.2.

6.4.1.3 ^{18}F FDG PET/CT Imaging

^{18}F FDG PET/CT imaging has been used as an exploratory measure of activity and inflammation in IgG4-RD patients. Baseline images will be obtained within 28 days before the first infusion of XmAb5871 and compared to images obtained at Day 85 (+/- 3 days) and at Day 169 (+/- 3 days). Stat serum pregnancy testing will be done on the day of the PET scan (during the screening period and at Days 85 and 169) and negative result documented prior to beginning the radiological procedure in women of child-bearing potential. PET will be performed with full diagnostic CT, and low-dose CT attenuation correction. The dosing of ^{18}F FDG will follow current clinical BMI-based protocol: 15mCi standard, 20mCi for BMI greater than 35, and 25mCi for BMI greater than 45.

6.4.1.4 Optional Tissue Biopsy

Patients may consent to an optional predose biopsy of involved tissue for pathology, immunohistology and potentially mechanistic studies prior to study drug administration. Patients may also elect to undergo an optional biopsy of involved tissues at any timepoint in the study after treatment begins if clinically indicated based on clinical response to treatment, i.e., improvement or worsening.

7 STUDY CONDUCT

7.1 Schedule of Assessments

The study consists of a Screening visit (Day -28 to Day -1) followed by twelve infusions of XmAb5871 given every two weeks (Days 1, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141 and 155) with collection of safety, 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 169 and 197[EOS]). The maximal study duration for an individual subject will be 197 days after the first infusion.

Please see Table 6 for the schedule of assessments:

Table 6: Schedule of Assessments

Study Phase	Screening	Treatment														EOS
VISIT NUMBER	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
WEEK		**1**	**2**	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**17**	**19**	**21**	**23**	**25**	**29**
DAY	**-28 to -1**	**1**	**8**	**15 +/-1**	**29 +/-1**	**43 +/-1**	**57 +/-1**	**71 +/-1**	**85 +/-3**	**99 +/-2**	**113 +/-2**	**127 +/-2**	**141 +/-2**	**155 +/-2**	**169 +/-3**	**197 +/-3**
Informed consent	X															
Study drug administration[1]		X		X	X	X	X	X	X	X	X	X	X	X		
Medical history	X	X														
Physical examination[2]	X[3]	X[3]	X	X	X		X		X		X		X		X[3]	X
Adverse Event assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead electrocardiogram[5]	X	X			X		X				X			X		X
CBC w/ differential, platelet count	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry Panel Tube 1-3	X	X		X	X		X		X		X		X		X	X
PT/INR and APTT	X	X	X		X				X				X			X
Urinalysis	X	X			X				X				X			X
Urine Pregnancy test[6]	X	X						X								X
HBsAg, HBcAb, HCV, HIV I and II Ab[7]	X															
Serum follicle stimulating hormone (FSH; (postmenopausal females only)	X															
Serum immunoglobulin levels (IgM, IgE, IgG, IgA, IgG_{1-4} subclasses)	X	X	X	X	X		X		X		X		X		X	X
C3 and C4	X	X		X	X		X		X		X		X		X	X
B and T cell quantitation; CD19 RO		X	X	X	X		X		X		X		X		X	X
Absolute B cell count [8]	X															
Plasmablast enumeration and mechanistic studies	X	X[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Phase	Screening	Treatment														EOS
VISIT NUMBER	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
WEEK		**1**	**2**	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**17**	**19**	**21**	**23**	**25**	**29**
DAY	**-28 to -1**	**1**	**8**	**15 +/-1**	**29 +/-1**	**43 +/-1**	**57 +/-1**	**71 +/-1**	**85 +/-3**	**99 +/-2**	**113 +/-2**	**127 +/-2**	**141 +/-2**	**155 +/-2**	**169 +/-3**	**197 +/-3**
FcγR polymorphism genotyping (FcγRIIa R131H and FcγRIIb I232T)		X[10]														
Pharmacokinetic blood sampling		X[11]	X	X[11]	X[11]	X[11]		X[11]		X[11]		X[11]		X[11]	X	X
Immunogenicity (ADA) blood sampling[12]	X	X			X			X		X				X	X	X[13]
IgG4-RD RI	X	X		X	X		X		X		X		X		X	X
Physician and patient Global Activity VAS	X	X		X	X		X		X		X		X		X	X
Stat serum pregnancy test [14]	X								X						X	
^{18}F FDG PET/CT imaging	X[14]								X[14]						X[14]	
Tissue Biopsy (optional)[15]	X									X[15]						

[1] XmAb5871 to be given over 2 hours for the first infusion, then over 1-2 hours for subsequent infusions.

[2] Include height at screening only and weight on all dosing days.

[3] Complete physical examinations will be performed at Screening and on Days 1 and 169. Abbreviated, symptom directed PE will be performed on Days 8, 15, 29, 57, 85, 113, 141, and 197 (EOS).

[4] Supine blood pressure and heart rate, body temperature, respiratory rate. 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 [±5 minutes]), and at 15, 30, 60 and 120 minutes after EOI (±5 minutes). 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 [±5 minutes]), and at 30 and 60 minutes after EOI(±5 minutes). On non-dosing days vital signs should be measured prior to blood sampling.

[5] Supine ECG immediately prior to infusion and 2 hours after end-of-infusion on Day 1. All others to be done pre-dose.

[6] Pregnancy test only for women of child-bearing potential (urine)

[7] If the patient has a documented negative result within 60 days before the first dose of XmAb5871, this item may be omitted.

[8] Only for patients with a history of rituximab (or other anti-CD20 mAb) use

[9] Mechanistic study sample predose, 2 hours and 24 hours (optional) after end-of-infusion.

[10] Sample to be collected pre-dose.

[11] PK pre-infusion and at end of infusion

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

[13]Patients with a positive ADA at EOS (or early termination) will be followed every 28 days (± 3 days) until ADA is negative.

[14] Stat serum pregnancy testing will be done on the day of the PET scan (during the screening period and at Days 85 and 169) and negative result documented prior to beginning the radiological procedure in women of child-bearing potential.

[15]An optional biopsy of clinically involved tissue may be performed during screening or up to predose Day 1. Patients may also elect to undergo an optional repeat of the involved tissues at any time point in the study after treatment begins if clinically indicated based on clinical response to treatment, i.e., improvement or worsening.

7.1.1 Assessments by Visit

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

7.1.2 Early Termination Visit

If a subject withdraws prematurely, all assessments as listed for the Day 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 197/EOS visit should be performed.

7.1.3 End-of-Study

End-of-Study is defined as completion of the End-of Study Visit on Day 197. Patients with a positive ADA at end-of-study will be followed every 28 days (± 3 days) until ADA is negative. For those patients that withdraw prematurely see Section 7.1.2. In addition, the PI and/or study site will contact all patients approximately every 6 months following EOS and will keep a log of when (if) the patient has recurrent symptoms and when (if) new medications for IgG4-RD treatment have been added since the end of study. This information will be provided to the sponsor periodically following the completion of the study.

8 STATISTICAL METHODS

Before database lock, a statistical analysis plan (SAP) will be issued as a separate document, providing detailed methods for 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 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 assigned an enrollment number), 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. All efficacy and safety analyses will utilize the intent-to-treat analysis dataset.
- Safety Population: All patients who receive at least a partial dose of XmAb5871. In this study, this was 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

Since this is an open-label, single-arm clinical trial, descriptive 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 medians and Kaplan-Meier plots. 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 and safety analysis will be performed on the ITT/Safety Population which is defined as all patients who received any amount of XmAb5871.

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

Since this is an open-label pilot Phase 2 study to investigate the effect of XmAb5871 on IgG4-RD disease activity, an appropriate sample size cannot be statistically determined since adequate information is not available to perform formal sample size calculations.

The sample size chosen for this study was based upon precedent set by other pilot studies of similar nature and was not based on power calculations. The sample size is based primarily on feasibility and the desire to gain efficacy and safety information to support further clinical studies. A total of approximately 21 patients are considered suitable to achieve the study objectives.

8.4 Treatment Assignment and Blinding

This is an open-label, single-arm, phase 2 study; thus, blinding is not part of the study design.

8.5 Study Endpoints and Statistical Analyses

Efficacy analyses will be performed on ITT Population.

8.5.1 Primary Efficacy Endpoint (Disease Activity)

The primary endpoint will be the proportion of patients on Day 169 with an improvement of disease activity score as defined by a decrease of IgG4-RD RI (Total Activity Score) of ≥2 points from Day 1 pre-dose disease activity score. The number of "responders" will be presented as frequency counts and percentages.

8.5.2 Secondary Efficacy Endpoint (Disease Activity)

The Total Activity Score (from the IgG4-RD RI) will be summarized 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. For those patients that respond (per the primary endpoint) the duration of improvement will also be presented. Additional analyses on the different RI parameters will be described in the SAP.

Physician Global Assessment of Disease Activity (Visual Activity Score) and Patient Global Assessment of Disease Activity (Visual Activity Score) will be summarized 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.

The proportion of patients with 1) a decline of the IgG4-RD RI of ≥ 2 points compared to baseline (Day 1), 2) no glucocorticoid use between Day 57 and Day 169, and 3) no disease flares during the study will be determined. Disease flare is defined as increase in the IgG4-RD RI of ≥ 2 and/or the need for increase in steroids or institution of additional therapy for IgG4-RD. The number of patients meeting the combination of these three criteria will be presented as frequency counts and percentages at all timepoints.

8.5.3 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. Treatment-emergent adverse events will also be tabulated according to intensity and causality.
- 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. 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) 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.
- Physical Examinations will be presented in patient listings.

8.6 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).

8.7 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.

8.8 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, IgG4 and IgE serum levels, total plasmablasts 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.

8.9 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.

8.10 Immunogenicity Analysis

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

8.11 Interim Analyses

No formal interim analysis is planned, however as this is an open-label study, continuous review of safety and efficacy data will occur may be used 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 may 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 TMG. 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 subject 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 a telephone number 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 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 subject 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 receive IRB approval prior to implementation (as appropriate). Where the deviation occurs for the well-being of the subject, the Sponsor must be informed of the action agreed upon.

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 subject number, initial or birth date, not by name. Documents that identify the subject (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 IgG4-RD Responder Index (IgG4-RD RI)

The IgG4-RD RI is a tool designed to detect change in disease activity and identify improvements and worsening in the same or different organ systems (modified after Carruthers, 2012).

At each assessment, the physician enters a 0-3 score after the organ/site listed with;

0 = Normal or resolved

1 = Improved but still present

2 = New or recurrent disease activity while patient is off treatment, or unchanged from previous visit*

3 = Worsened or new disease manifestation despite treatment

*Unchanged from previous visit will often refer to disease manifestations that require follow-up imaging to assess accurately.

The second column is used to record symptomatic disease; yes=Y, no=N.

The third column records whether there is urgent disease in that site; yes=Y, no=N.

Damage in the organ/site is recorded in the fourth column; yes=Y, no=N.

The fifth column records whether damage in the organ/site is symptomatic; yes=Y, no=N.

Physician Global Assessment of disease activity is denoted on a 100 mm line as covered further in Appendix 11.1.2.

IgG4-RD Responder Index (Version 25July2016)

Scoring Rules

Scoring refers to manifestations of disease activity present in the last 28 days

Scoring: 0 Normal or resolved
1 Improved but still present
2 New / Recurrence while patient is off treatment or unchanged from previous visit*
3 Worsened or new disease manifestation despite treatment

*Unchanged from previous visit will often refer to disease manifestations that require follow-up imaging to assess accurately

Definitions

Organ/Site score: The overall level of IgG4-RD activity within a specific organ system

Symptomatic: Is the disease manifestation in a particular organ system symptomatic? (Y = yes; N = no)

	Activity			Damage	
Organ/Site	Organ/Site Score (0-4)	Symptomatic (Yes/No)	Urgent (Yes/No)	Yes/No	Symptomatic (Yes/No)
Meninges					
Pituitary Gland					
Orbital lesion (specify location): _____					
Lacrimal Glands					
Parotid Glands					
Submandibular Glands					
Other Salivary Glands (specify): _____					
Mastoiditis / Middle ear disease					
Nasal Cavity Lesions					
Sinusitis					
Other ENT Lesions, e.g., tonsillitis, pharyngitis (specify): _____					
Thyroid					
Lungs					
Lymph Nodes (please circle site of involvement, below):					
Submental Submandibular Cervical Axillary Mediastinal Hilar Abdominal/Pelvic Inguinal Other lymph node chains:					

	Activity			Damage	
Organ/Site	Organ/Site Score (0-4)	Symptomatic (Yes/No)	Urgent (Yes/No)	Yes/No	Symptomatic (Yes/No)
Aorta / Large Blood Vessels					
Heart/Pericardium					
Retroperitoneal Fibrosis					
Sclerosing Mediastinitis					
Sclerosing Mesenteritis					
Pancreas					
Liver					
Bile ducts					
Kidney					
Skin					
Constitutional symptoms not attributable to involvement of a particular organ (weight loss, fever, fatigue caused by active IgG4-RD)					
Other involvement - specify: (Consider prostate, breast, gallbladder involvement; and other. Each "Other" item is counted separately.) _____ _____	_____ _____	_____ _____	_____ _____	_____ _____	_____ _____

Total Activity Score

Organ/sites (x 2 if urgent): _____

Total **urgent** organs: _____

Total **symptomatic (active)** organs: _____

Total **damaged** organs: _____

Total **symptomatic (damage)** organs: _____

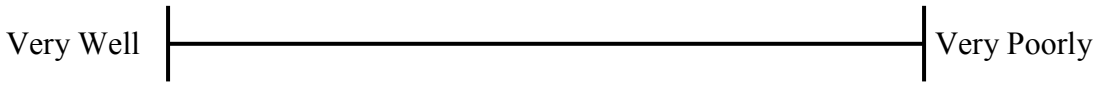
Total activity score is calculated as given in the lower left hand corner =

Sum of organ scores (any that are urgent are multiplied by 2).

11.1.2 Physician and Patient Global Assessment of Disease Activity (VAS)

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

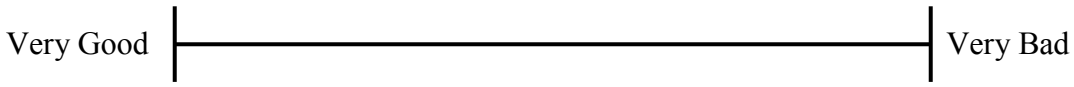
The patient will be instructed as follows: Considering all the ways in which illness and health conditions may affect you at this time, please make a mark between 0 and 100 mm on the line below to show how you are doing:



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

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

Place a mark on the line below to indicate disease activity (independent of the patient's self-assessment):



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