STATISTICAL ANALYSIS PLAN

Study Title:	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
Name of Test Drug:	XmAb5871
Protocol Number:	XmAb5871-03
Phase:	Phase 2
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STATISTICAL ANALYSIS PLAN APPROVAL

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ABBREVIATIONS AND DEFINITIONS

Ab	antibody
ABC	absolute B cell count
ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
AP	alkaline phosphatase
ATC	anatomical therapeutic chemical
BMI	body mass index
bpm	beats per minute
BP	blood pressure
BUN	blood urea nitrogen
CI	confidence interval
CPK	creatine phosphokinase
CRF	case report form
CS	clinically significant
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DBP	diastolic blood pressure
ECG	electrocardiogram
eCRF	electronic case report form
EOI	end of infusion
EOS	end-of-study
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
Fv	antibody variable
GCP	Good Clinical Practices
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
ICH	International Committee for Harmonization
Ig	immunoglobulin
IgG4-RD	IgG4-Related Disease
IP	Investigational Product
IQR	interquartile range

IU	international units
IV	intravenous
K-M	Kaplan-Meier
LDH	lactate dehydrogenase
mAb	monoclonal antibody
mmHg	millimeters of mercury
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NCS	not clinically significant
PD	pharmacodynamic
PK	pharmacokinetic
PT	preferred term
PPT	partial prothrombin time
RI	Responder Index
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis Software
SBP	systolic blood pressure
SD	standard deviation
SE	standard error of the mean
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
UNK	unknown
VAS	Visual Analog Scale
WHO-DD	World Health Organization - Drug Dictionary

1. INTRODUCTION

The Statistical Analysis Plan (SAP) describes the data analysis specifications for Xencor, Inc. protocol XmAb5871-03 titled: "*An Open-label, Single-arm Pilot Study to Evaluate the Effect of XmAb®5871 on Disease Activity in Patients with IgG4-Related Disease*". It details the inferential statistical methodology to be used in analyzing study data and outlines the statistical programming specifications, tables, figures, and listings. It describes the variables and populations, anticipated data transformations and manipulations, and other details of the analyses not provided in the clinical study protocol. Additional purposes of the SAP are to serve as a communication tool between Vantage Data Designs, Inc. and Xencor, Inc.with respect to expected statistical data outputs after database lock and to allow SAS programming of the tables, listings, figures to commence as early in the process as possible.

This version of the statistical analysis plan was prepared in accordance with the protocol XmAb5871-03 Version 3 Amendment 2, dated January 31, 2017. Other related documents are the electronic case report forms (eCRFs), Medidata RAVE Screen Shots DEV Draft v3.1, and Medidata RAVE System Data Specifications (SDS) document dated 30NOV2015. This SAP supersedes the statistical considerations identified in the protocol. The SAP will be finalized prior to database lock and describes the statistical analysis as it is foreseen when the study is being planned. If circumstances should arise during the study rendering this analysis inappropriate, or if in the meantime improved methods of analysis should come to light, different analyses may be made. Any deviations from the SAP after database lock, including alternative or additional statistical analyses that may be performed, will be described in the clinical study report.

2. OVERVIEW OF STUDY DESIGN

Experimental Design: Phase 2, multi-center, non-randomized, open-label, pilot study in patients with active IgG4-Related Disease (IgG4-RD).

Allocation of treatment: single agent (XmAb5871) – no randomization. There are two cohorts for this study: 5 mg/kg (first 15 subjects), fixed 90 mg or 180 mg (up to 6 additional subjects).

Number of patients planned: a total of up to 21 patients will be enrolled at at the Massachusetts General Hospital (Boston, MA) and up to 2 additional sites in the United States. Patients who are lost to follow up or withdraw consent for study participation prior to study drug administration may be replaced, at sponsor's discretion.

Treatment and 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.

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.

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. These up to 6 additional patients will be pooled as a second cohort ("Fixed Dose"). At the discretion of the Investigator and Sponsor, patients 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 patients will be administered over a 1 hour period at a constant rate.

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 patient will be 197 days after the first infusion. See Section 13 of this statistical analysis plan for more details.

Data collection: Electronic Case Report Form (eCRF).

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 Objectives

- 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 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 18F FDG PET/CT imaging in patients with active IgG4-RD.

3. SAMPLE SIZE JUSTIFICATION

Approximately 21 patients will be enrolled in this study. 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, patients dosed at 90 mg of XmAb5871 may have their dose increased to 180 mg if there has been an inadequate clinical response to therapy.

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. Therefore, the sample size is based primarily on feasibility of study conduct and the desire to gain information to support further clinical studies. Approximately 21 patients are considered to provide sufficient initial information on the 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 IgG-4-RD before the initiation of a randomized, double blind placebo controlled study in this disease.

4. RANDOMIZATION, BLINDING, AND REPLACEMENT OF PATIENTS

This is a single-arm, open-label study with the identity of the treatment (XmAb5871) and dose group known to the patients, Investigators, and Sponsor; therefore, no randomization or blinding procedures will be performed.

Patients who are lost to follow-up or withdraw consent for study participation prior to administration of study drug may be replaced, at sponsor's discretion.

5. DEFINITIONS OF PATIENT POPULATIONS TO BE ANALYZED

The populations defined below may be subdivided into patients with a starting dose of 5 mg/kg versus those starting at a fixed dose (i.e. 90mg or 180mg) and any affected analyses will be labelled accordingly.

5.1 Enrolled Population

Defined as 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.

5.2 Efficacy Population

Defined as all patients who received at least a partial dose of XmAb5871. All efficacy and safety analyses will utilize the efficacy analysis dataset.

5.3 Safety Population

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

5.4 Pharmacokinetic/Immunogenicity Population

Defined as 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.

5.5 Pharmacodynamic Population:

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

6. DEFINITIONS, COMPUTATIONS, DATA CONVENTIONS

6.1 Definitions and Computations

Screening

Screening is defined as Day -28 to Day -1 (Visit 1) prior to the first study drug administration.

Baseline

Baseline represents the procedures or assessments done prior to the first administration of XmAB5871 at Day 1 (Visit 2) captured in the EX dataset.

Visit Dates

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

Study Phase	**Day**
Screening	**-28 to -1**
Treatment	**1, 8, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, 169**
End of Study	**197**
Discontinue Study Early	**Safety – 2 week and Safety – 6 Week**

Safety – 2 Week and Safety – 6 Week time points

If a patient 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.

The new time points are designed to summarize patients that prematurely withdrew from the study. These early termination patient assessments (per above paragraph) will be mapped to two new visits, 'Safety – 2 Week' and 'Safety – 6 week'. These visits will be ordered last on by-visit summary table outputs after Day 169 and Day 197. Consequently, the Day 169 and Day 197 visits will summarize data only for subjects who have completed the study.

Adverse Event (AE)

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

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

Treatment Emergent Adverse Event (TEAE)

Adverse medical events occurring after the Date of Informed Consent but before the first dose of study drug will be recorded on the Medical History form. Therefore, all AEs captured on AE dataset are considered "treatment-emergent" adverse events (TEAEs).

Efficacy Endpoints

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

Safety Endpoints

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

6.2 Conventions

- 1 year = 365.25 days. Year is calculated as (days / 365.25) and will be rounded to 1 digit after the decimal point (tenths) for presentation purposes.
- 1 month = 30.4375 days. Month is calculated as (days / 30.4375) and will be rounded to 1 digit after the decimal point (tenths) for presentation purposes.
- 1 pound = 0.454 kg and 1 kg = 2.2 pounds
- 1 inch = 2.54 cm and 1 cm = 0.3937 inches
- Body mass index (BMI) calculated as [weight (lbs) / height $(in)^2$] x 703
- BMI using metric system: [weight (kg) / $[height (m)]^2$
- Age will be calculated in years relative to the date of study consent based on the following SAS statement: Age = ([Consent Date - Date of Birth] / 365.25) and will be rounded to 1 digit after the decimal point (tenths) for presentation purposes.
- The software used for all summary statistics and statistical analyses will be SAS Version 9.4 or later.
- All tables, listings, figures will be produced in landscape orientation using Times New Roman 9 point font. Output files will be created in rich text file (RTF) format.
- Missing or invalid data will be generally treated as missing, not imputed, unless otherwise stated (see Section 7).

7. MISSING DATA AND DROPOUTS

The issue of how to handle missing data caused by dropouts in clinical studies is a research topic that is still under development in the statistical literature. As has been noted in the ICH-E9 guideline, “no universally applicable method of handling missing values can be

recommended". The best approach is to minimize the chance of dropouts at the design stage of the clinical study and during study monitoring.

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

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

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

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

Imputed dates will be noted in the patient data listings.

7.2 Partial/Missing Dates for Adverse Events

Adverse events with incomplete start dates will be considered treatment-emergent adverse events (TEAEs), if:

- Onset time is missing but the onset date is on Study Day 1;
- Day and month are missing and the year is equal to or after the year of the first date of study drug dosing;
- Day is missing and the year is after the year of the first date of study drug dosing;
- Day is missing and the year is equal to the year of the first date of study drug dosing and the month is equal to or after the month of the first date of study drug dosing; or
- Year is missing.

8. DESCRIPTION OF STATISTICAL ANALYSES

8.1 General Principles

Unless otherwise noted, data will be summarized in tabular format using summary tables and data listings grouped by XmAb5871 5 mg/kg versus XmAb5871 Fixed Dose (i.e. 90 mg or 180 mg). Data summaries will only include patients that receive study drug. All study data documented on the eCRFs will be included in the study data listings.

Given this is a Phase 2 single-agent, open-label study without a control arm, no formal testing for confirmatory purposes planned; however, if any statistical tests are utilized they will be two-sided, with type 1 error rate of 5%, unless otherwise noted. All confidence intervals (if constructed) will be constructed at the 95% confidence level, unless otherwise noted. Any inferential statistical tests performed for this study are considered exploratory in nature; therefore, no p-value adjustments for multiplicity analyses will be made.

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

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

8.2 Patient Enrollment, Disposition, Protocol Deviations

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

8.3 Demographics

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

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

8.4 Baseline Characteristics

A summary of various patient baseline characteristics such as: time from onset of signs/symptoms, time from last remission, serum IgG4 levels, histologies, IgG4 characteristics (i.e., positive staining, plasmablasts, plasmablasts ratio), received prior systemic therapy for IgG4 related disease (yes, no), type(s) of prior therapy, and best response to prior therapy will be displayed using appropriate descriptive statistics.

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

8.5 Physical Examination and Medical History/Concurrent Illness

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

8.6 Prior and Concomitant Therapy

All medications taken within 30 days prior to screening will be listed as prior medications in patient listings. All medications taken since the time of dosing until the end of the study will be classified as concomitant medications. These medications will be coded using WHO Drug Dictionary (WHO DD), version September 2015. The number and proportion of patients in the Safety population using concomitant medications will be tabulated and summarized in a table by WHODrug anatomic therapeutic chemical class (ATC) and preferred drug name. These data will also be presented in patient listings.

8.7 Study Treatment Administration, Exposure

Exposure to XmAb5871 will be demonstrated by calculating the days of exposure (date of first dose of XmAb5871 to the last dose date of XmAb5871) and the number of infusions. These will be tabulated by dose groups using descriptive statistics.

Patient listings will be prepared showing the patient number, lot number, and the date and time of dose administration, total volume/dose administered, planned volume/dose, dose interruptions, and reason for dose interruption.

8.8 Efficacy and Exploratory Analysis

The Efficacy Population defined as as all patients who received at least a partial dose of XmAb5871 will be utilized for all efficacy and exploratory analyses. Efficacy data will be summarized in tabular format by XmAb5871 dose group.

8.8.1 Primary Efficacy Endpoint

Disease Activity per IgG4-Related Disease Responder Index (IgG4-RD RI)

Disease activity will be measured at Screening and on Days 1, 15, 29, 57, 85, 113, 141, 169, and 197 (EOS). For determination of IgG4-RD responders, the IgG4-RD responder index (IgG4-RD RI) of Carruthers et al. 2012 will be used, with modification as specified in the protocol.

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. Patients without IgG4-RD RI Total Activity Score improvement of ≥2 points (from Day 1 pre-dose disease activity) score at Day 169 or not assessed at Day 169 will be considered a non-responder for purposes of this analysis.

The number of "responders" will be presented as frequency counts and percentages. The Clopper Pearson exact 95% two-sided confidence interval will be constructed around the estimated proportion of patients who achieve a response to therapy as defined in previous paragraph.

8.8.2 Secondary Efficacy Endpoints

8.8.2.1 Response Time

Response time will be defined as the time (days) from first dose to the date of the first IgG4-RD RI improvement of ≥2 (from Day 1 pre-dose disease activity) within 169 days.

The number of patients meeting this criterion will be presented as frequency counts and percentages. For those patients that achieve a response, the time to response will be summarized using descriptive statistics (mean, standard deviation, median, minimum value, and mximium value). For those patient that did not achieve a response, the amount of follow-

up time (days from first dose to latest efficacy assessment) will be described descriptively (mean, standard deviation, median, minimum value, and maximium value).

8.8.2.2 Duration of Response and Loss of Response

Definitions include:

- Loss of response: Defined as any patient with an initial response who subsequently reports an RI increase of ≥2 points from the previous visit.
- Loss of response time (for patients with loss of response): Days from date of first RI response to the date of loss of response.
- Follow-up time (for censored patients): Days from date of first RI response to date of last assessment (i.e. last assessment date – date of first response + 1).
- Duration of Response (Follow-up time – Overall): Estimated distribution of the time from initial RI response to loss of response, accounting for censoring using the Kaplan-Meier method.

The number of patients with loss of response will be presented as frequency counts and percentages. Loss of response time and follow-up time will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum/maximum).

Duration of response will be summarized using Kaplan-Meier methods. The summary statistics (N, minimum, Kaplan-Meier median, maximum, number censored) will be displayed to characterize duration of improvement.

8.8.2.3 Disease Activity Combination Assessment (IgG4-RD-RI, No Glucocorticoid, No Disease Flare) Assessment

The proportion of patients at Day 169 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,

3) no disease flares during the study. 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 all three of the criteria listed above will be presented as frequency counts and percentages. The Clopper Pearson exact 95% two-sided confidence interval will be constructed around the estimated proportion of patients who achieve a response (meeting all three criteria above).

8.8.2.4 The Total Activity Score (from the IgG4-RD RI)

The Total Activity Score will be summarized at each visit using descriptive statistics (N, mean, standard deviation, median, minimum/maximum). Change from baseline and percent change from baseline will also be tabulated at each visit using the same descriptive statistics.

Additional subgroup exploratory analyses on the different RI organ assessments will be assessed and undertaken (if appropriate) at the time of data analysis as guided by the overall RI results. These will be described in detail within the clinical study report.

8.8.2.5 Disease Activity: Visual Analog Scale

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 "none" (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).

Physician and Patient Global Assessment VAS will be summarized at each visit using descriptive statistics (N, mean, standard deviation, median, minimum/maximum). Change from baseline and percent change from baseline will also be tabulated at each visit using the same descriptive statistics.

8.8.3 Exploratory Efficacy Endpoints

^{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. Individual patient listings of the results from the PET/CT Scans will be provided.

8.9 Safety Analysis

Safety Population is defined as all patients who received at least a partial dose of XmAb5871 and will be utilized for all safety analyses. In this study the Safety Population is equivalent to the EFFICACY population. The safety data will be summarized in tabular format by XmAb5871 dose group using summary tables.

8.9.1 Treatment Emergent Adverse Events

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

Adverse medical events occurring after the Date of Informed Consent but before the first dose of study drug will be recorded on the Medical History form. Thereafter all AEs captured on AE dataset will be considered "treatment emergent" adverse events.

Verbatim terms of TEAEs will be mapped to preferred terms and related system organ classes (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0.

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

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

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

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

8.9.2 Serious Adverse Events

A listing of patients who reported a serious adverse event will be included. The data will be obtained from the adverse events eCRF, including all events with the SAE boxed checked, and separately from the safety reporting database. These two datasets (SAE and Safety Reporting) will be reconciled prior to database lock.

8.9.3 Adverse Events Leading to Discontinuation from Study

A listing of patients and the adverse events which led to study discontinuation from the study will be included. The specific AE will be identified from the EOS dataset where the primary

reason for treatment termination is checked as an Adverse Event. The AE number from the EOS dataset will link back to the AE dataset to identify the specific AE leading to discontinuation from study.

8.9.4 Adverse Events Leading to Dose Modifications

A listing of patients with adverse events that led to a dose modification will be included. The specific AE leading to a dose modification will be identified from the AE dataset where "Action Taken" for either study drug is: Dose Interrupted, Dose Decrease, Slowed Infusion Rate, Hospitalization or prolongation of hospitalization required, Dose Discontinued.

8.9.5 Deaths Due to Adverse Event

A listing of patients who died on study will be included. The specific AE will be identified from the DEATH dataset. If primary or secondary cause of death is an AE, the AE number from the DEATH dataset will link back to the AE dataset to identify the specific AE leading to death.

8.9.6 Clinical Laboratory Tests

Hematology will be assessed at Screening and at Days 1, 8, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, 169, and 197 and include the following: 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 will be assessed at Screening and at Days 1, 8, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, 169, and 197 and include the following: Tube 1: total protein, sodium, potassium, calcium, chloride, bicarbonate (HCO3), 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).

Urinalysis will be assessed at Screening, and on Days 1, 29, 85, 141, and 197 (microscopic urinalysis will be performed if urinalysis results are abnormal).

Coagulation parameters (international normalized ratio (INR), prothrombin time (PT), and activated partial thromboplastin time (aPTT)) will be assessed on Screening, and Days 1, 8, 29, 85, 141, and 197.

Immunoglobulin (Serum IgG, IgE, IgM, IgA and IgG1-4) 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.

Summary statistics (n, mean, SD, median, min, max) will be utilized to characterize hematology, clinical chemistry, coagulation, immunoglobulin, and complement levels and will be presented by Visit and Timepoint. Corresponding change from baseline and percent change from baseline will also be presented for the hematology, clinical chemistry, coagulation, immunoglobulin, and complement levels tests.

Shift tables (shift from baseline grade to maximum and minimum post-dose grade) will be presented for hematology, clinical chemistry, coagulation, immunoglobulin, and complement levels tests. Urinalysis parameters will be presented in patient listings. The results from urine Pregnancy tests (Screening, Days 1, 71 and 197), Follicle Stimulating Hormone (assessed at Screening only), and Serology (assessed at Screening only) will be presented in patient listings.

Individual patient data listings of all hematology, clinical chemistry, coagulation, urinalysis, serum immunoglobulins and complement level results will be presented by patient and time point. All values outside the clinical reference ranges will be flagged in the data listings. The abnormal values will be flagged with 'Low' for values below the lower limit of the clinical reference range and 'High' for values above the upper limit of the clinical reference range and included in the listings. The investigator will assess whether the values outside the clinical reference range are clinically significant and these will be reported as abnormal not clinically significant (NCS) or abnormal clinically significant (CS). Clinically significant laboratory values will be recorded by the Investigator as AEs. Two separate listings will be generated for abnormal laboratory values and for CS laboratory values, with grouping by type of laboratory assay (i.e. hematology, clinical chemistry, coagulation, urinalysis, serum immunoglobulins and complement level).

8.9.7 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).

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

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

8.9.8 12-Lead Electrocardiogram

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 patient has been resting supine for ≥ 5 minutes.

The following ECG parameters will be collected: PR interval, QRS interval, RR interval, QT interval, and QTc interval (QTcB and QTcF).

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

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

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

and categorized according to their change from baseline into the categories

- ≤ 30 ms,

- 30 – 60 ms
- 60 ms

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

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

8.10 Pharmacodynamics

Flow Cytometry Laboratory tests will be collected on Days 1, 8, 15, 29, 57, 85, 113, 141, 169, and 197. Analyses will include B cell CD19 Fluorescence Intensity (MESF) and both absolute counts (cells/uL) and percentages (%) for the following B cell subsets: B cells (CD20+), B cells CD19+, B cells IgD+CD27+, B cells IgD+CD27-, B cells IgD-CD27+, B cells IgD-CD27-.

Summary statistics (n, mean, SD, median, min, max) will be utilized to characterize the flow cytometry laboratory parameters and will be presented by Visit and Timepoint. Corresponding change from baseline and percent change from baseline will also be presented for these parameters. Individual patient data listings of these flow cytometry tests will be presented by patient and time point.

8.11 Pharmacokinetics

XmAb5871 pharmacokinetic visit, scheduled time point, sampling dates/times will be listed by patient.

8.12 Pharmacogenomics

The date/time (if not done, reason why) of the pharmacogenomics evaluation (FcγR polymorphism genotyping) will be listed by patient. These data will be analyzed by an appropriate expert consultant in this field.

8.13 Immunogenicity: Anti-drug Antibodies (ADA)

Individual patient data listings of anti-drug antibodies (ADA) will be displayed.

9. SOFTWARE SYSTEM

Statistical Analysis Software (SAS) version 9.4 or later will be used to analyze the data, create summary tables, patient data listings, and graphical representation of the data.

10. INTERIM ANALYSIS

No formal interim analysis is planned, however as this is an open-label study, continuous review of safety and efficacy data will occur and may be used for submission to regulatory authorities.

11. STATISTICAL ANALYSIS CHANGES FROM THE PROTOCOL

The analyses described are based on the final clinical study protocol XmAb5871-03 Version 3.0 Amendment 2, 31 Jan 2017. This SAP supersedes the statistical considerations identified in the protocol.

12. REFERENCES

1. Protocol XmAb5871-03: An Open-label, Single-arm, Pilot Study to Evaluate the Effect of XmAb®5871 on Disease Activity in Patients with IgG4-Related Disease. Version 3 Amendment 2, January 31, 2017.
2. International Federation of Pharmaceutical Manufacturers and Associations. Medical Dictionary for Regulatory Activities (MedDRA). Version 17.1 Reston, Virginia, USA; 2008.
3. WHO Collaborating Center for International Drug Monitoring. WHO Drug Dictionary. December 2014 Format edition. Uppsala, Sweden; 2008.
4. SAS Institute Inc. SAS Version 9.4. Cary, NC, USA; 2002-2003.
5. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.
6. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.

13. SCHEDULE OF ASSESSMENTS

Study Phase	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

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.

14. LABORATORY COLLECTION, DATA ANALYSIS, AND TABLES/LISTINGS

Endpoint Type	Laboratory Type	Collection Source (Organization)	Data Analysis	Tables/Listings
Safety	Chemistry	eCRF (MGH)	VDD	VDD to provide table/listing
Safety	Hematology	eCRF (MGH)	VDD	VDD to provide table/listing
Safety	Urinalysis	eCRF (MGH)	VDD	VDD to provide table/listing
Safety	Microscopic Urinalysis (only if urinalysis results abnormal)	eCRF (MGH)	VDD	VDD to provide listing
Safety	Coagulation: PTT, aPTT, INR	eCRF (MGH)	VDD	VDD to provide table/listing
Safety (exclusion test)	Pregnancy Test and FSH (screening only)	eCRF (MGH)	VDD	VDD to provide listing
Safety (exclusion test)	Serology (Screening only, see below)	eCRF (MGH)	VDD	VDD to provide listing
Safety	Immunoglobulin (see below)	eCRF (MGH)	VDD	VDD to provide table/listing
Safety	Complement (C3 and C4)	eCRF (MGH)	VDD	VDD to provide table/listing
Immunogenicity	Anti-drug Antibodies: ADA	External ICON Development Sol.	Dan Combs (Consultant)	VDD to provide listing
Pharmacokinetics	Pharmacokinetics	External: ICON Development Sol.	Dan Combs (Consultant)	VDD to provide listing
Pharmacodynamics	Flow Cytometry: B-cell and T-cell Quantitation and CD19	External: ICON Central Labs	Dan Combs (Consultant)	VDD to provide table/listing
Pharmacodynamics	Absolute B-cell count (CD3+, CD3+CD4, CD3+ CD8)	eCRF (MGH)	Dan Combs (Consultant)	VDD to provide table/listing
Pharmacodynamics	IgE and IgG4	eCRF (MGH)	Dan Combs (Consultant)	VDD to provide table/listing
Pharmacodynamics	Plasmablast/Mechanistic	External: Ragon Institute of MGH	Ragon	VDD to provide listing
Pharmacogenomics	FcγR polymorphism genotyping	External: Gentris Corp.	Gentris	VDD to provide listing
Disease Activity	PET/CT imaging	External: MGH: Dr.Sahani,	Xencor	VDD to provide listing

Clinical Safety Laboratory Source: Pathology Core Laboratory of the Massachusetts General Hospital (MGH) and results on eCRF.