A Randomized, Double-blind, Placebo-controlled, First-in-Human Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of a Single Intravenous Infusion of XTMAB-16 in Healthy Adult Participants

Protocol Number: XTMAB-16-101

IND Number: 143210

Principal Investigator: Ron Goldwater, MDCM, MSc(A)

Sponsor: Xentria Inc.

Version Number: 4.0 (Amendment 3)

28 May 2021

Amendment 3: Summary of Changes from Previous Version (version 3.0 dated 14 May 2021):

Affected Section(s)	Summary of Revisions Made	Rationale
Cover Page, Investigator's Agreement, 1.1 Synopsis	Study title updated to remove "two-part".	Updated in response to FDA request dated 28 May 2021.
1.1 Synopsis, 1.2 Schema, 1.3 Schedule of Activities, 3 Objectives and Endpoints, 4.1 Overall Design, 4.1 Dose Escalation, 4.3 Justification for Dose, 5.5 Replacement of Participants, 9.2 Sample Size Determination, 9.4.6 Planned Safety Review	Study design updated and "two-part" and relevant description on Part A and Part B removed. The number of cohorts updated from 4 to 2 (now Cohorts 1 and 2), and the total number of participants updated to 24 (12 participants each cohort). Dose of each cohort updated to 2 mg/kg for Cohort 1, and 4 mg/kg for Cohort 2. Study objective updated to reflect the dose. The randomization ratio of participants except for sentinel cohort updated to 4:1. Justification for dose updated accordingly to reflect the revised dose.	Updated in response to FDA request dated 28 May 2021.
6.1.2 Dosing and Administration	Reference to the Pharmacy Manual added, and the dose of each cohort updated.	To refer to the Pharmacy Manual for details. Updated in response to FDA request dated 28 May 2021.

Amendment 2: Summary of Changes from Previous Version (version 2.0 dated 11 March 2021):

Affected Section(s)	Summary of Revisions Made	Rationale
Sponsor Signature Page	Updated Sponsor Signature Page: Remove [redacted] and add [redacted]	Xentria staff changes.
1.1 Synopsis	Updated study description to remove dosage details for Cohort 3 and Cohort 4 (6 and 10 mg/kg become x and y mg/kg) Added additional detail to explain Part B study start. Upon completion of Part A, PK modeling will be used to determine Part B's dosing regimen for Cohort 3 and 4. Clarify that Part B will not resume enrollment until a full review of safety and PK are submitted, reviewed, and approved by FDA.	Updated in response to FDA Full Clinical Hold Letter dated 31 March 2021.
1.2 Schema	Update Study Schematic to remove Part B dosage details. Replace 6 and 10 mg/kg with x and y mg/kg.	Updated in response to FDA Full Clinical Hold Letter dated 31 March 2021.
1.3 Schedule of Assessments	Provided additional detail in footnote k regarding data collection procedures. Administrative correction footnote l.	Change made to accommodate site's standard of care and per IRB Clarification Letter (February 2021).
2.2.3 XTMAB-16	Updated the result of completed study.	13-week pre-clinical work completed and study data is updated.
2.2.4 Toxicology Overview	Updated the result of completed study.	13-week pre-clinical work completed and study data is updated.

Affected Section(s)	Summary of Revisions Made	Rationale
4.1.2.1 Criteria 6.5.1 Rescue Medication	Corrected Appendix 5 to Appendix 4 Corrected Appendix 6 to Appendix 5	Administrative correction.
4.1 Overall Design	Updated study description to remove dosage details for Cohort 3 and Cohort 4 (6 and 10 mg/kg become x and y mg/kg) Added additional detail to explain Part B study start. Upon completion of Part A, PK modeling will be used to determine Part B's dosing regimen for Cohort 3 and 4. Clarify that Part B will not resume enrollment until a full review of safety and PK are submitted, reviewed, and approved by FDA.	Updated in response to FDA Full Clinical Hold Letter dated 31 March 2021.
Section 3 Objectives	Update Objectives to remove dosage details. Replace 6 and 10 mg/kg with x and y mg/kg.	Updated in response to FDA Full Clinical Hold Letter dated 31 March 2021.
4.1 Overall Design 4.1.1 Dose Escalation	Updated study description to remove dosage details for Cohort 3 and Cohort 4 (6 and 10 mg/kg become x and y mg/kg) Added additional detail to explain Part B study start. The study will be paused for any further enrollment after Cohort 2 has completed all follow-up visits. A full safety analysis of and PK report will be submitted to the FDA for review and approval to move forward with higher doses in Part B. The same protocol design will be repeated for Part B (Cohort 3 and Cohort 4).	Updated in response to FDA Full Clinical Hold Letter dated 31 March 2021.

Affected Section(s)	Summary of Revisions Made	Rationale
	Update Table 2 dose chart (removed 6 and 10 mg/kg and replace with x and y mg/kg) Provide Part B information: PK modeling will determine doses to be tested in Cohorts 3 and 4. Reiterate that Part B will not begin until FDA approval.	
4.3 Justification for Dose	Update the planned dosage for Part B, 6 and 10 mg/kg with x and y mg/kg. Justification for dose updated based on the completed 13-week GLP TgTC toxicology study.	Updated in response to FDA Full Clinical Hold Letter dated 31 March 2021.
5.2 Exclusion Criteria	Corrected Exclusion #21 lab values to align with Exclusion #12.	Updated in response to FDA Information Request (IR) dated 08 March 2021.
5.3 Lifestyle Considerations	Clarify subject position for vital signs. A semi-supine position during infusion.	Change made to accommodate site's standard of care and per IRB Clarification Letter (February 2021).
6.2.2 Formulation, Appearance, Packaging, and Labeling	The reconstituted solution is stable at room temperature for ≤4 hours. The reconstituted solution should be stored at 5° C or at room temperature prior to administration for ≤4 hours. This information is also detailed in the pharmacy manual.	Updated in response to FDA Full Clinical Hold Letter dated 31 March 2021.
6.2.2 Formulation, Appearance, Packaging, and Labeling 6.3.2 Preparation	The information on the appearance updated from "colorless to pale-yellow and clear" to "colorless to pale-yellow and opalescent".	Administrative correction.

Affected Section(s)	Summary of Revisions Made	Rationale
	KBMAB-16 replaced with XTMAB-16	
6.2.3 Product Storage and Stability	Update infusion timing. Infusion should begin within 1.5 hours of reconstitution and dilution.	Updated based on shortened IP stability at room temperature.
6.3.1.1 Unblinding Procedure	Corrected header numbering and hyperlinks/references from 6.3.1.1 to 6.3.1	Administrative correction.
6.5 Concomitant Therapy (Table 4)	Corrected "study" to "study drug (XTMAB16 or placebo).	Administrative correction.
8.2.3 Vital Signs 8.2.4 Electrocardiograms	Clarify subject position for data collection. Semi-supine/semi-reclined during infusion, supine for all other timepoints.	Change made to accommodate site's standard of care and per IRB Clarification Letter (February 2021).
Section 10.1.5 Key Roles and Study Governance (Table 6)	Study team update: [redacted] removed [redacted] added [redacted] AD, Clinical Operations removed [redacted] Clinical Affairs Manager added	Updated to capture staff changes.

Amendment 1: Summary of Changes from Previous Version (version 1.0 dated 19 Jan 2021):

Affected Section(s)	Summary of Revisions Made	Rationale
Protocol Title Change	Added "Two-part" to title.	Title change to clarify that the study would be conducted in 2 phases, with an FDA review of safety and PK data following completion of Part A, in response to FDA position on NOAEL and

Affected Section(s)	Summary of Revisions Made	Rationale
		Information Request (IR) dated 08 Mar 2021.
Synopsis (Study Description), Section 1.3, Section 2.3, Section 4.1, Section 6.1.2, Section 6.5	Removed pretreatment with 500 mg acetaminophen.	Updated in response to FDA IR dated 08 Mar 2021. Participants will instead be closely monitored and treated symptomatically. Additional guidance has been added assessing and treating anaphylaxis.
Synopsis (Study Design, Study Population, Phase, Study Duration, Sample Size, Description of Study Intervention, Section 4.1, Section 4.3	Text added that the study would be conducted in 2 phases (Part A and Part B). Part A will consist of the lower dose cohorts (1 and 3 mg/kg) and Part B will consist of the higher dose cohorts (6 and 10 mg/kg). The study will be paused after completion of Part A and an interim analysis of the data will be provided to the FDA. Upon approval to proceed, Part B will be initiated. Both phases will be conducted identically with the same Schedule of Assessments.	Per FDA IR of 08 Mar 2021: Amended study design for conducting the FIH study in 2 parts, including FDA review of the data following completion of Part A. This allows assessment of safety and PK data from human participants at a level consistent with the preclinical NOAEL before proceeding to higher doses in humans.
Section 1.3, Appendix 1 (Table 7)	New footnotes that tryptase levels will be assessed for all participants at Baseline, and additionally if a participant experiences anaphylaxis within 4 hours after completion of infusion.	Added in response to FDA IR dated 08 Mar 2021. Provides guidance for detailed monitoring of any anaphylactic response.
Section 1.3, Section 6.5	Footnotes to clarify the timing of COVID-19 vaccination. The COVID-19 vaccine may be given up to 30 days prior to Day1 dosing, or at any time through study after the Week 4 assessments are complete.	Added in response to FDA IR dated 08 Mar 2021.

Affected Section(s)	Summary of Revisions Made	Rationale
	Additionally, at each visit a temperature check will be performed and participants will be asked if they have been exposed to someone known to have COVID-19. Temperatures over 100°F (37.7°C) will trigger an unscheduled COVID-19 test.	
Section 2.3, Section 6.5.1, Appendix 4, Appendix 5	Text added regarding injection site reactions to be graded according to a new Appendix 4 added for toxicity grading (Grades 1-4) related to severity. Added text that appropriate personnel and medications for treating hypersensitivity reactions should be available, and added a new Appendix 5 for diagnosing and treating anaphylaxis.	Updated in response to FDA IR dated 08 Mar 2021. Participants will instead be monitored closely and treated symptomatically. Additional guidance has been added assessing and treating anaphylaxis.
Section 4.1.2.1	Text added text for stopping infusion related to injection site reactions and/or anaphylaxis. Reactions of Grade 3 or higher will indicate termination of infusion.	Updated in response to FDA IR dated 08 Mar 2021. Participants will instead be monitored closely and treated symptomatically.
Section 4.2.1.2, Section 9.4.2.1	Text added to clarify stopping rules in the event of liver function tests meeting Hy's Law and the analysis of liver function test results.	Updated in response to FDA IR dated 08 Mar 2021. While liver function tests were included as part of the protocol, the added text provides specificity.
Section 4.3, Table 3	Removed Human PK simulation data from Table 3	Updated in response to FDA IR dated 08 Mar 2021.
Section 5.1, Inclusion criterion #6, Appendix 3	Clarified that women of childbearing potential are eligible for enrollment. Clarified that restrictions for reproductive safety risks extend	Updated in response to FDA IR dated 08 Mar 2021. Addressed existing discrepancies.

Affected Section(s)	Summary of Revisions Made	Rationale
	through 90 days after dosing. Clarified that highly effective methods of contraception are to be used. Updated the list of highly effective contraception.	
Section 5.2, Exclusion criterion #12	Added specific criteria and acceptable normal limits for liver and renal laboratory screening and enrollment parameters.	Updated in response to FDA IR dated 08 Mar 2021. Parameter limits were not previously specified.
Section 6.5, Table 4	Clarified that prescription contraceptives and short-term antibiotics are allowed, that medications in the table are prohibited from the time shown through Day 8, and clarified COVID-19 vaccinations.	Per FDA IR dated 08 Mar 2021.
Section 9.4.6	Interim analysis statement corrected as per revised study design; data after completion of Part A will be analyzed and summarized.	Correction related to change in study design and to clarify that the study would be conducted in 2 phases, including FDA review of the safety and PK data after Part A has been completed, in response to FDA IR dated 08 Mar 2021. This allows assessment of safety and PK data from human participants at a level consistent with the preclinical NOAEL prior to proceeding to Part B with higher doses evaluated in healthy volunteers.

SPONSOR SIGNATURE PAGE

I confirm that I have read and approved this protocol in its entirety and will comply with the obligations as detailed in all applicable regulations and guidelines (eg, International Council on Harmonisation [ICH] Good Clinical Practice [GCP] guidelines) and the protocol.

[redacted] 2 June 2021

[redacted] Date

Chief Medical Officer

Xentria Inc.

[redacted]

[redacted]

INVESTIGATOR'S AGREEMENT

PROTOCOL TITLE: A Randomized, Double-blind, Placebo-controlled, First-in-Human Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of a Single Intravenous Infusion of XTMAB-16 in Healthy Adult Participants

PROTOCOL NUMBER: XTMAB-16-101

VERSION: Amendment 3

This protocol is a confidential communication of the Sponsor. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCPs and all applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study center in which the study will be conducted. Return the signed copy to the Sponsor or designee.

I have read this protocol in its entirety and agree to conduct the study accordingly.

Signature of Investigator	Date

Ronald Goldwater, MDCM, MSC(A), CPI
Principal Investigator

Name/Address of Center:	Parexel Baltimore Early Phase Clinical Unit
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	Baltimore, MD 21115

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with ICH GCP, applicable United States (US) Code of Federal Regulations (CFR), and applicable local regulations. The Principal Investigator will ensure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) Sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: A Randomized, Double-blind, Placebo-controlled First-in-Human Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of a Single Intravenous Infusion of XTMAB-16 in Healthy Adult Participants

Study Description: This is a single-center, randomized, double-blind, placebo-controlled, first-in-human, single intravenous (IV) infusion of sequential ascending doses of XTMAB-16 (formerly referred to as KBMAB-16) in normal healthy male and female participants.

A total of 24 normal healthy adult participants will be enrolled and assigned into 2 treatment cohorts with 12 participants (9 on XTMAB-16 and 3 on placebo) in each cohort.

Cohort	Dose[a]	Escalation Factor	XTMAB-16	Placebo[a]	Total
1	2 mg/kg	-	9	3	12
2	4 mg/kg	2 x	9	3	12

a The matching placebo will be identical to the XTMAB-16 in terms of volume and infusion duration.

For all cohorts, a sentinel group of 2 participants (1 assigned to XTMAB-16 and 1 assigned to placebo) will be dosed at least 48 hours before the remaining participants in the same cohort. After blinded review of the available safety and laboratory data of the sentinel group by the Principal Investigator (PI), if no notable safety signals are identified, the remaining participants within the same cohort will be dosed. Participants within a cohort should be dosed at least 1 hour apart.

If there are no safety concerns after completion of Cohort 1, the participants at cohort 2 will receive XTMAB-16 after 14 to 21 days clinical assessment of the participants at cohort "n-1."

After a screening period of up to 28 days, participants will be admitted to the clinical research unit (CRU) on Day -2 for COVID-19 testing and baseline procedures. After confirmation of eligibility, participants will be randomly assigned to treatment (1:1 XTMAB-16 to placebo for sentinel cohort, 4:1 for remaining participants) and administered study drug on Day 1. Participants will remain at the CRU through Day 8 for pharmacokinetics (PK), biomarkers, anti-drug antibodies (ADA), and safety assessments, and will be discharged on Day 8 once all procedures for that day have been

completed. Participants will return to the CRU on Days 15, 29, 43, 57, and 71 (End of Study/safety follow-up).

Safety assessments will include adverse events (AEs), safety laboratory assessments, vital signs, electrocardiogram (ECG), immunogenicity, and physical examination. PK collection and analysis will also be completed in a similar manner during the course of this study.

Objective: To evaluate the safety, tolerability, immunogenicity, PK, and selected clinical biomarkers after a single intravenous infusion of XTMAB-16 at 2 and 4 mg/kg doses in normal healthy participants.

Endpoints:

Safety and Tolerability

- The incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
- Observed values and change from Baseline in safety laboratory tests (hematology, clinical chemistry, urinalysis) by visit
- Observed values and change from Baseline in ECG by visit
- Time-matched Baseline and 50-hr postdose digital ECG monitoring
- Observed values and change from Baseline in vital signs

Immunogenicity

- Number and percentage of participants by cohort who test positive for XTMAB-16 ADA at Baseline, Day 29, Day 57, and Day 71
- Number and percentage of participants by cohort who test positive for XTMAB-16 nAb at Baseline, Day 29, Day 57, and Day 71

Pharmacokinetics

- Maximum observed XTMAB-16 concentration (C_{max})
- XTMAB-16 serum concentration at the end of drug infusion (C_T)
- Time to maximum observed XTMAB-16 concentration (t_{max})
- Area under the XTMAB-16 concentration-time curve from time zero (predose) extrapolated to infinity ($AUC_{0-\infty}$)
- Area under the XTMAB-16 concentration-time-curve from time zero to (predose) to the last quantifiable time point at t (AUC_{0-t})
- Systemic clearance after IV dosing (CL)
- Apparent terminal half-life ($t_{1/2}$)
- Volume of distribution following IV dosing (V_z)
- Mean residence time (MRT)

	Biomarkers
	• Absolute and percent change from Baseline in the following biomarkers
	  ○ Angiotensin converting enzyme (ACE)
	  ○ Soluble IL-2 receptor (sIL-2R)
	  ○ Interleukin 6 (IL-6)
	  ○ Soluble tumor necrosis factor (sTNFα)

Study Population:	A total of 24 male and female healthy adult participants aged 18 to 45 years, inclusive.
Phase:	1
Description of Sites/Facilities Enrolling Participants:	This study will be performed at a single CRU in the US.
Description of Study Intervention:	XTMAB-16 is a chimeric human-murine IgG1κ anti-TNFα monoclonal antibody. The final dosage form is a sterile, white, lyophilized powder for IV infusion. Participants assigned to active treatment will receive a single dose of XTMAB-16 at a volume of 250 mL via IV infusion over 2 hours. The total dose received will be either 2 or 4 mg/kg, depending on treatment assignment. Placebo will be the same formulation as the active treatment, but without XTMAB-16. Participants assigned to placebo will receive a single dose of placebo at a volume of 250 mL via IV infusion over 2 hours.
Study Duration:	Study duration is expected to be approximately 4-5 months from First Patient First Visit to Last Patient Last Visit.
Participant Duration:	The study consists of an up to 28-day screening period, a 57-day treatment period, and a 14-day follow-up period, for a total duration of participation of up to 99 days.
Statistical Methods	**Sample size**: The selection of 24 participants was based on feasibility, first-in-human (FIH) guidelines, industry standards, and empirical considerations. No sample size calculation was performed. **Analysis Datasets:** • The Enrolled Set (ES) will consist of all participants who have given informed consent. • The Full Analysis Set (FAS) will consist of all participants randomized into the study.

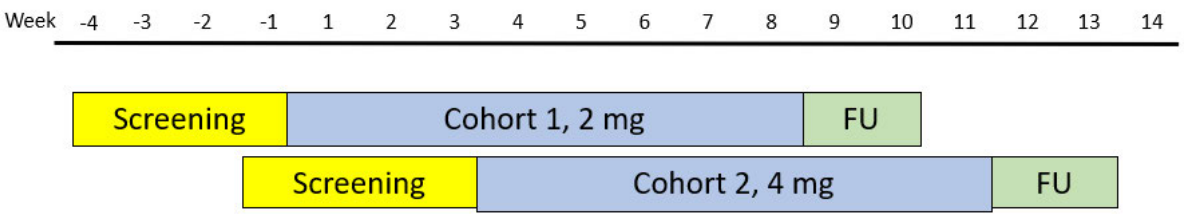
- The Safety Set: will consist of all study participants who are randomized and have received at least 1 dose of study medication.
- The Pharmacokinetic Per-Protocol Set (PK-PPS) consists of all participants in the Safety Set who provide at least 1 quantifiable serum XTMAB-16 PK sample postdose without important protocol deviations that would affect the concentration.
- Biomarker Set will consist of all participants in the PK-PPS who have at least 1 postdose biomarker measurement.

Statistical Analysis:

All safety, tolerability, laboratory, PK, biomarkers, and immunogenicity data will be summarized and listed using descriptive statistics.

1.2 SCHEMA

Figure 1 Study Schematic



Abbreviations: FU = follow-up.

1.3 SCHEDULE OF ASSESSMENTS

Table 1 Schedule of Assessments

	Screening	Baseline		Treatment Period													EOS
Week	-4 to -1			1								2	3	4	6	8	10
Day	-28 to -3	-2[a]		1				2	3	4		8	15	29	43	57	71
Window	-	-	-		-	-	-	-	-	-	-	-	±24 hrs	±24 hrs	±24 hrs	±24 hrs	±3 days
PK Hour (from start of infusion)			0	1	2(T)	3	8	14	24	50	74	170	338	674	1010	1346	1682
Informed consent	X																
Inclusion/exclusion	X	X															
Demographics	X																
Medical history	X	X															X
Physical examination[b]	X	X	X									X	X	X	X		X
Height	X																
Weight	X	X															
Serum pregnancy test[c]	X	X													X		X
Urinalysis	X	X										X	X	X	X	X	X
HIV, HBsAg, HCV, COVID-19[d], TB	X	COVID-19 Only															
Urine drug abuse screen[e]	X	X															
Participant confinement[f]		X															
Vital signs[g,h]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
ECG[g,k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Telemetry[k]		X															
Biochemistry[g,l]	X	X	X						X	X	X	X	X	X	X	X	X
Hematology[g]	X	X	X						X	X	X	X	X	X	X	X	X
PK[g,i,l]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Biomarkers[g,j]			X				X		X	X	X	X	X	X	X	X	X
ADA/nAb[m]			X									X	X	X	X	X	X
Infusion of study drug				X													
Concomitant medications	X	X										X	X	X	X	X	X
Adverse events	X	←														→	

Abbreviations: ACE = angiotensin converting enzyme; ADA = anti-drug antibody; ECG = electrocardiogram; EOS = end of study; FU = follow-up; HBsAg = hepatitis B antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IL-6 = interleukin 6; nAb = neutralizing antibodies; PK = pharmacokinetics; sIL-2R = soluble IL-2 receptor; sTNFα = soluble tumor necrosis factor alpha; TB = tuberculosis.

a Assessments at Day -2 may be performed on Day -1, as needed, by the clinical research unit, but must be performed no later than Day -1.

b A full physical examination will be performed at Screening, Baseline, Day 8, and Day 71. An abbreviated physical examination will be performed predose on Day 1, and Days 15, 29, and 43. See Section 8.2.1 for a description of the physical examination.

c For women of childbearing potential only. At Baseline, an FSH test will be run to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or hormone replacement therapy.

d At each visit, participants will have a temperature check and will be asked if they have had exposure to someone known to have COVID-19. If the temperature is above 100°F (37.7°C) or the answer is "yes," participants will be tested for COVID-19. Participants who receive a COVID-19 vaccine prior to study entry must receive the final vaccine at least 30 days before dosing and will be tested for COVID-19 as per the SoA. Participants who wish to receive the COVID-19 vaccine after dosing must wait until after Week 4 PK sampling and other assessments have been completed. COVID-19 vaccination and any adverse reaction to the vaccine must be reported.

e This will include a blood draw to test for blood alcohol levels.

f From check-in at Day -2 to discharge from the unit on Day 8. Since the participants will be immunocompromised by administration of study treatment, the participants should be instructed to quarantine at home for 6 days after discharge from the clinical research unit.

g When a meal, vital signs, ECG, or blood sample collection are scheduled at the same time as the study drug administration, the following order will be respected: ECG, vital signs, clinical biomarkers, PK, ADA, safety laboratory samples, and meal. To respect exact timing of PK samples (see Table 8), the other measurements will be done ahead of the scheduled time. The assessment schedule should be adapted to the design of the study.

h During infusion, blood pressure and heart rate should be collected every 15 minutes for the first hour, every 30 minutes for the second hour, and hourly for 2 hours after the completion of infusion.

i Blood samples will be collected for XTMAB-16 PK analysis at predose (Hour 0), at 1 hour after the start of infusion, 1 hour after the start of infusion, immediately after the 2-hour infusion (T; infusion termination), and at 3, 8, 14 hours on Day 1, and at 24 hours (Day 2), 50 hours (Day 3), 74 hours (Day 4), 170 hours (Week 2, Day 8), 338 hours (Week 3, Day 15), 674 (Week 4, Day 29), 1010 (Week 6, Day 43), 1346 hours (Week 8, Day 57), and 1682 hours (Week 10, Day 71) postinfusion of XTMAB-16 or placebo. All sampling time points after time T refer to time from the start of infusion. Acceptable windows for PK sample collection are provided in Table 8. The exact time of sample collection must be recorded on the eCRF.

j Blood samples will be collected to evaluate biomarker concentrations of ACE, sIL-2R, IL-6, and sTNFα.

k Single 12-Lead ECGs will be collected at all time points. Additional ECGs will be performed at the discretion of the Investigator. Telemetry recording will begin on Day -1 and continue through 50 hours after the start of infusion. At specified time points, for extraction of telemetry data, participants should be in a semi-reclined resting position for at least 10 minutes prior to the target time of data extraction (at least 15 minutes when coinciding with PK/ADA/nAb blood collection). On Day -1, resting periods for telemetry data extraction should occur at 1, 2, 3, and 8 hours (corresponding to the projected time points on Day 1). On Day 1, resting periods for telemetry data extraction should occur at predose (to match the time point for 24 hours after the start of infusion) and 1, 2, 3, 8, and 24 hours after the start of infusion. A resting period for telemetry data extraction will also occur at 50 hours after the end of infusion. During infusion, data will be collected in a semi-supine/semi-reclined position, and for all other readings, data will be collected in a supine position.

l Tryptase levels will be assessed at Baseline for all participants. For any participant who experiences anaphylaxis within 4 hours after the end of infusion, and additional sample for assessment of tryptase levels should be collected as soon as is reasonable. See Appendix 5 for diagnosis and treatment of anaphylaxis.

m Blood samples for PK/ADA/nAb will be collected for analysis from participants who experience an SAE that is also considered related to study treatment.

2 INTRODUCTION

2.1 STUDY RATIONALE

The purpose of the study is to evaluate the safety, tolerability, immunogenicity, and pharmacokinetics (PK) of single ascending intravenous (IV) doses of XTMAB-16 in healthy adult subjects. This study is the first time that XTMAB-16 will be administered to humans. The safety, tolerability and PK results obtained from this study will inform future clinical development of XTMAB-16 for the treatment of sarcoidosis.

[redacted]

XTMAB-16 is being developed as a monoclonal antibody (mAb) tumor necrosis factor alpha (TNFα) blocker to address the treatment gap for patients with advanced pulmonary sarcoidosis with or without extrapulmonary involvement.

2.2 BACKGROUND

2.2.1 SARCOIDOSIS

Sarcoidosis is a chronic systemic disease of unknown etiology and uncertain prognosis that most commonly affects young and middle-aged adults. Sarcoidosis is characterized by the presence of noncaseating granulomas in 1 or more organs. While sarcoidosis is a systemic disease, the lungs, lymphatic system, and skin are most commonly affected.[42] Patients frequently present with pulmonary infiltrates, bilateral hilar lymphadenopathy, and ocular and skin lesions.[8]

A widely accepted hypothesis of the pathogenesis of sarcoidosis is that various unidentified antigens, either infectious or environmental, trigger an exaggerated immune response in

genetically predisposed individuals.[3,36,42] In the lung, the antigen is presented to naive CD4+ lymphocytes and alveolar macrophages, activating both cell types, and subsequently triggers a complicated cascade of proinflammatory cytokines. The release of cytokines enhances the expression of tumor necrosis factor α (TNFα), a protein that plays a significant role in antigen-stimulated, cell-mediated immune responses.[7] High levels of TNFα released from alveolar macrophages have been shown to correlate with disease progression. [6,9] Notably, spontaneous release of TNFα by alveolar macrophages is greater in patients with active disease than in those with inactive or corticosteroid-treated disease.[50] Similar inflammatory mechanisms are believed to underlie sarcoidosis involvement in other organs, such as the skin.[20]

To prevent granuloma formation and limit tissue injury and fibrosis, targeted immunosuppression of proinflammatory cytokines such as TNFα is a clear goal of therapy, particularly in patients with chronic sarcoidosis.

Please see the Investigator's Brochure (IB) for additional details.

2.2.2 TNFα

TNFα is a proinflammatory cytokine widely recognized and implicated in inflammatory disorders including sarcoidosis.

A model for granuloma formation in sarcoidosis patients suggests that macrophages, dendritic cells, and lymphocytes, with the aid of cytokines and chemokines, collaborate with one another. TNFα, one of the participating cytokines in the formation of the sarcoid granuloma, along with the successful use of immunomodulators inhibiting TNFα such as pentoxiphylline and thalidomide, led to the increasing utilization of anti-TNF agents in sarcoidosis patients. In patients with severe refractory sarcoidosis who do not respond to conventional immunosuppressive treatment, TNFα inhibitors infliximab and adalimumab are recommended by the World Association of Sarcoidosis and other Granulomatous Disorders (WASOG).[12] Comparisons between TNFα inhibitors have shown that infliximab is superior to other anti-TNF therapies.[4,13,36]

[redacted]

Please see the IB for additional details.

2.2.3 XTMAB-16

XTMAB-16 is a chimeric human-murine IgG1κ anti-TNFα monoclonal antibody with a molecular weight of ~149 kDa. Extensive analyses have been conducted to demonstrate the physio-chemical properties and pharmacology of XTMAB-16 as a TNFα inhibitor.

[redacted]

In a Good Laboratory Practices (GLP) 13-week hTNF transgenic (TgTC) mouse toxicology study, the inhibitory effect of KBMAB-16 (clinical drug product XTMAB-16) as a TNFα blocker and its potential pharmacologic benefit were demonstrated by comparing the arthritis scores in joints of vehicle and test-article treated animals using both clinical observations and histopathological examinations. The study determined that there was statistically significant improvement in arthritis scores in the KBMAB-16 treated groups which received 10, 20, or 40 mg/kg of XTMAB-16 as compared to the vehicle control group, starting at week 5 (Day 36) until the end of the study at week 17 (p <0.01 or p <0.05).

XTMAB-16 is currently being developed as a novel biologic product for the treatment of patients with advanced pulmonary sarcoidosis with or without extrapulmonary involvement.

Clinical Overview

This will be the first clinical study ever performed for XTMAB-16. No previous clinical data are available for this study drug. [redacted]

[redacted]

Please see the IB for additional details.

2.2.4 TOXICOLOGY OVERVIEW

The 6-week GLP, TgTC mouse, toxicology study included: (1) a main (toxicity) study (60 animals, 10 /sex/dose; vehicle vs 20 mg/kg vs 40 mg/kg), with a 4-week treatment period followed by a 2-week recovery period, to evaluate the toxicity of KBMAB-16 (clinical drug product XTMAB-16) from 3 biweekly IV injections (Days 1, 15, 29); and, (2) a satellite (toxicokinetic [TK]) study

(132 animals, 2/sex/dose/time point for 10 time points) to characterize a single IV dose TK profile. The findings are summarized below.

KBMAB-16 was well tolerated up to 40 mg/kg after 3 biweekly IV injections. All animals survived in the toxicity study with no meaningful abnormal clinical and pathological findings. Thus, the no adverse effect level (NOAEL) of KBMAB-16/XTMAB-16 was considered to be 40 mg/kg via 3 biweekly IV injections in TgTC mice.

In the TK groups, a complete 6-week (1008 hours) TK profile following a single dose (10 mg/kg, 20 mg/kg and 40 mg/kg) of KBMAB-16 was obtained. After a single 40 mg/kg IV injection, the maximum observed concentration (C_{max}) was at 791.0 µg/mL and the area under the concentration-time curve $(AUC)_{0-\infty}$ was at 124257.2 µg∗hr/mL. The systemic exposure in terms of C_{max} and $AUC_{0-\infty}$ were increased proportionally in the dose range from 10 to 40 mg/kg of KBMAB-16. The half-life ($t_{1/2}$) of XTMAB-16 ranged from 9.4 days (226.9 hr) at 10 mg/kg to 13.6 days (327.2 hr) at 40 mg/kg, which is comparable to the half-life of 10 mg/kg of infliximab in humans of 13.9 days (335.1 hr).[21]

In a 13-week, repeated dose, GLP, toxicology study (Study 14042-20005) in hTNFα transgenic mice, KBMAB-16 was well tolerated up to 40 mg/kg after 7 bi-weekly IV injections in TgTC animals in the toxicity study with no meaningful test article related clinical and pathological abnormalities observed. The NOAEL of KBMAB-16 was considered to be 40 mg/kg after 7 doses biweekly IV injection in TgTC mice. In addition, safety pharmacology assessments of the central nervous system (CNS) and respiratory systems did not reveal adverse effects at any dose of KBMAB-16. After 40 mg/kg IV injection for 6 doses, the C_{max} was 1104.9 µg/mL, the $(AUC)_{0-\infty}$ was 624865.9 µg∗hr/mL and the $(AUC)_{0-\tau}$ was 124878.7 µg∗hr/mL. The systemic exposure in terms of C_{max} and $(AUC)_{0-\infty}$ increased in a dose proportional matter in the dose range from 10 to 40 mg/kg of KBMAB-16.

For further detailed nonclinical data for XTMAB-16, refer to the IB.

Risk/Benefit Assessment

This is the first time that XTMAB-16 will be administered to humans. XTMAB-16 is not expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate safety, tolerability, immunogenicity, and PK data to provide the basis for further clinical development of XTMAB-16 as a potential new, pharmacological agent for the treatment of sarcoidosis. As such, data from this study may benefit people with sarcoidosis in the future.

As of the issuance of this protocol, no specific human risks have been identified based on data gathered during a nonclinical study with XTMAB-16 using a transgenic mouse model (see IB). The clinical impact of any potential risks will be minimized through cautious dose escalation; that is, higher doses of XTMAB-16 will be administered only after lower doses have been found to be well tolerated with an acceptable safety profile. In addition, this study includes standard, intensive, inpatient monitoring of the participants following administration of single, IV doses of the investigational product. Clinical safety laboratory tests, thorough assessments of vital signs,

electrocardiograms (ECGs), physical examinations, and adverse event (AE) monitoring will provide essential data to evaluate the safety and tolerability of XTMAB-16 in humans.

TNFα blockers have been extensively studied and their risks are well characterized. The known risks of TNFα blockers are similar across the drug class.[18,21] According to the TNFα blocker package inserts, the most significant risks [noted as a black box warning] include:[33]

- Serious infection or sepsis (including tuberculosis, histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, pneumocystosis, Legionella, and Listeria)
- Malignancy (including hepatosplenic T cell lymphoma)

To reduce the risk of infection or sepsis in this study, healthy participants without active infections will be enrolled. Additionally, participants with a medical history of conditions known to be at risk for AEs with TNFα blockers (eg, tuberculosis, hepatitis) or who have lived in or traveled to areas of endemic tuberculosis or endemic mycoses are excluded from participation.

While malignancy cannot specifically be prevented or reduced, most of the patients who reported malignancies after taking TNFα blockers were also taking concomitant immunosuppressants. In this study of healthy participants, participants requiring immunosuppressants will be excluded, thus the Sponsor considers the risk of malignancy in this study to be very low.

Additional contraindications noted for TNFα blockers include:

- Patients with moderate to severe heart failure (for doses >5 mg/kg)
- Patients with severe hypersensitivity reactions to infliximab products or components.

To mitigate the risk to patients with moderate to severe heart failure, participants with known cardiac conditions will be excluded from this study and all participants will be closely monitored for 2 hours after infusion (and up to 4 hours at the Investigator's discretion). Participants will be closely monitored for 2 hours after infusion (up to 4 hours at Investigator discretion). Injection site reactions will be graded according to Table 9. Hypersensitivity reactions, including any instances of anaphylaxis, will be monitored and treated as noted in Appendix 5. Given the above precautions for this study, the Sponsor considers the risk of cardiac conditions and hypersensitivity in this study to be low.

[redacted]

Taking into account that (1) XTMAB-16 is a TNFα blocker, a class of drug with a known safety profile, and (2) the measures taken to minimize risk to participants of this study, the potential

risks identified in association with XTMAB-16 are justified by the anticipated benefit, in terms of contribution to the process of developing new therapy in an area of unmet medical need.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
To evaluate the safety, tolerability, immunogenicity, PK, and selected clinical biomarkers after a single IV infusion of XTMAB-16 at 2 and 4 mg/kg doses in normal healthy participants.	<u>Safety and Tolerability</u> The incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) Observed values and change from Baseline in safety laboratory tests (hematology, clinical chemistry, urinalysis) by visit Observed values and change from Baseline in ECG by visit Time-matched Baseline and 50-hr postdose digital ECG monitoring Observed values and change from Baseline in vital signs <u>Immunogenicity</u> Number and percentage of participants by cohort who test positive for XTMAB-16 ADA at Baseline, Day 29, Day 57, and Day 71 Number and percentage of participants by cohort who test positive for XTMAB-16 nAb at Baseline, Day 29, Day 57, and Day 71 <u>Pharmacokinetics</u> Maximum observed XTMAB-16 concentration (C_{max}) XTMAB-16 serum concentration at the end of drug infusion (C_T) Time to maximum observed XTMAB-16 concentration (t_{max}) Area under the XTMAB-16 concentration-time curve from time zero (predose) extrapolated to infinity ($AUC_{0-\infty}$)	The endpoints chosen for this study are standard and commonly accepted for Phase 1 FIH trials to establish initial safety, PK, and immunogenicity in the support of continued investigation of the study drug for clinical development.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	Area under the XTMAB-16 concentration-time-curve from time zero to (predose) to the last quantifiable time point at t (AUC_{0-t}) Systemic clearance after IV dosing (CL) Apparent terminal half-life ($t_{1/2}$) Volume of distribution following IV dosing (V_z) Mean residence time (MRT) <u>Biomarkers</u> Absolute and percent change from Baseline in the following biomarkers • Angiotensin converting enzyme (ACE) • soluble IL-2 receptor (sIL-2R) • Interleukin 6 (IL-6) • soluble TNFα (sTNFα)	

Abbreviations: ACE = angiotensin converting enzyme; ADA = anti-drug antibody; IL-6 = interleukin 6; IV = intravenous; PK = pharmacokinetics

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a single-center, randomized, double-blind, placebo-controlled, first-in-human (FIH), single IV infusion of sequential ascending doses of XTMAB-16 in normal healthy male and female participants.

A total of 24 normal healthy adult participants will be enrolled and assigned into 2 treatment cohorts with 12 participants (9 on XTMAB-16 and 3 on placebo) in each cohort as shown in Table 2. Participants will receive a single intravenous (IV) infusion of 2 or 4 mg/kg of XTMAB-16 or placebo on Day 1.

Table 2 Dose Cohorts

Cohort	Dose	Escalation Factor	XTMAB-16	Placebo[a]	Total
1	2 mg/kg	-	9	3	12
2	4 mg/kg	2 x	9	3	12

a The matching placebo will be identical to the XTMAB-16 in terms of volume and infusion duration.

For all cohorts, a sentinel group of 2 participants (1 assigned to XTMAB-16 and 1 assigned to placebo) will be dosed at least 48 hours before the remaining participants in the same cohort. To maintain the treatment blind, study treatment will be prepared by an unblinded pharmacist according to the treatment assignment who will appropriately label the study drug for administration in a way that maintains the treatment blind to clinical research unit (CRU) staff and the participant.

After blinded review of the available safety and laboratory data of the sentinel group by the Principal Investigator (PI), if no notable safety signals are identified, the remaining participants within the same cohort will be dosed. Participants within a cohort should be dosed at least 1 hour apart. If there are no safety concerns, the participants in cohort 2 will receive XTMAB-16 after at least 14 to 21 days clinical assessment of the participants at cohort 1. See Section 4.1.1 for additional information on dose escalation.

After a screening period of up to 28 days, participants will be admitted to the CRU on Day -2 for COVID-19 testing and baseline procedures. After confirmation of eligibility, participants will be randomly assigned to treatment (1:1 XTMAB-16 to placebo for sentinel cohort, 3:1 for remaining participants) and administered study drug on Day 1. Participants will remain at the CRU through Day 8 for PK, biomarkers, ADA, and safety assessments, and will be discharged on Day 8 once all procedures for that day have been completed. Participants will return to the CRU on Days 15, 29, 43, 57, and 71 (End of Study/safety follow-up).

Safety assessments will include AEs, safety laboratory assessments, vital signs, ECG, immunogenicity, and physical examination. PK collection and analysis will also be completed in a similar manner during the course of this study.

4.1.1 DOSE ESCALATION

For all cohorts, a sentinel group of 2 participants (1 assigned to XTMAB-16 and 1 assigned to placebo) will be dosed at least 48 hours before the remaining participants in the same cohort. After blinded review of the available safety and laboratory data by the PI, if no notable safety signals are identified, the remaining participants within the same cohort will be dosed. Participants within a cohort should be dosed at least 1 hour apart.

As XTMAB-16 is a TNFα inhibitor, which have well-characterized clinical safety profiles, it can be given to participants in the 4 mg/kg dose group after 14 to 21 days clinical assessment of the participants at 2 mg/kg dose group, unless safety concerns arise.

Dose escalation will be stopped as soon as safety signals or risks are identified or anticipated, based on:

- Number of abnormal and clinically significant safety laboratory results
- Number of SAEs and/or TEAEs with severity/intensity high enough for a meaningful decision
- Proportion of TEAEs of the same type high enough to justify the decision

The severity rating is adapted to healthy participants, taking into account event characteristics such as type, deleterious potential, occurrence, progression, and monitorability. A solitary SAE occurrence is not by itself a criterion for making a decision (assessment depends on the nature of the reported event). See Section 4.1.2 for details on stopping rules.

A decision to proceed from dose “n” to the next higher “n+1” dose will be made jointly by the Sponsor and the Investigator based on a preliminary Investigator blinded safety report inclusive of the 12 participants in dose level cohort “n”. The relevant data for this decision should be, at a minimum, AEs, liver and kidney function tests, ECG, blood pressure, and heart rate.

For safety purposes, the treatment of a specific participant may be unblinded before the next dose level is administered, after mutual agreement between the Sponsor and the Investigator.

An unscheduled PK sample collection and analysis may be performed to support the clinical safety assessment, if needed in the event of a safety signal of concern.

Depending on the tolerability profile and safety laboratory results observed in the dose level cohort “n,” one of the following decisions will be made for cohort “n+1”:

- Dose escalation may continue as scheduled.

- A higher intermediate dose between the current dose ("n") and the next planned dose ("n+1") may be administered to the next cohort.
- A lower intermediate dose between the current dose ("n") and the previous dose ("n-1") may be administered to the next cohort, including the possibility of administering a dose lower than the starting dose.
- The study may be stopped.

4.1.2 STOPPING RULES

4.1.2.1 CRITERIA

Participants who experience injection site reactions or vital signs changes of Grade 1 or 2 (see Appendix 4) during infusion may continue infusion or have infusion interrupted for treatment and then resumed, at the discretion of the Investigator. Participants who experience injection site reactions or vital signs changes of Grade 3 or 4 during infusion should have infusion terminated and will be treated, as needed, for the adverse events. Any participant who experiences anaphylaxis during infusion will have infusion terminated; diagnosis of and recommended treatment for anaphylaxis is provided in Appendix 5.

In addition to the assessment of SAEs and the occurrence/severity of other AEs by the Sponsor and the Investigator, after exploring potential confounding factors, the following criteria should be considered as guidance for the decision to stop dose escalation or to stop administration of the study drug to additional participants:

- 1 SAE for which the relationship to treatment cannot be reasonably excluded
- 1 AE of severe intensity for which the relationship to treatment cannot be reasonably excluded
- 3 or more participants with AEs of moderate intensity for which the relationship to treatment cannot be reasonably excluded
- 1 participant in a cohort with potential Hy's Law values
    - ALT or AST >8 × upper limit of normal (ULN)
    - ALT or AST >5 × ULN for more than 2 weeks
    - ALT or AST >3 × ULN and (total bilirubin >2 × ULN or INR >1.5)
    - ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- QTcF ≥500 ms (men and women)
- Any other clinically significant intolerance findings

If any of the above occur, the Contract Research Organization (CRO) and Sponsor should be notified within 24 hours of becoming aware of the event. Decisions to stop dose escalation or stop administration of study drug to additional participants will be determined collectively between the PI, CRO Medical Monitor, and Sponsor.

4.1.2.2 ACTIONS

At each dose level, if 1 of the above criteria is met at that dose level, the treatment blind will be broken by the Sponsor for the concerned participants as follows:

- If 3 or more participants were given XTMAB-16 and no participant was given placebo, drug administration will be stopped for these participants and all other participants in that dose level; and either
  - One or more lower dose(s) may be considered, only if, after reviewing all data, the Investigator and the Sponsor agree that it is safe to do so, or
  - Study may be stopped.
- Otherwise, drug administration per protocol may either continue as planned or be reconsidered if, after reviewing all data, the Sponsor and the Investigator agree that it is safe to do so; and either
  - The current dose level may be continued, or
  - One or more lower dose(s) may be considered, or
  - The study may be stopped

The drug administration per protocol may either continue as planned or be reconsidered only if, after reviewing all data, the Sponsor and the Investigator agree that it is safe to do so.

The treatment blind may be broken for other reasons, supported by a clear rationale.

The Investigator and Sponsor may decide to stop study drug administration based on other safety signals not described in the above criteria.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The design of this Phase 1, SAD clinical trial is similar to other FIH studies evaluating TNFα inhibitors.[39]

Based on TK results in the 6-week, GLP, toxicology study in hTNFα transgenic (TgTC) mice, the half-life ($t_{1/2}$) of XTMAB-16 ranged from 9.4 days (226.9 hr) at 10 mg/kg to 13.6 days (327.2 hr) at 40 mg/kg, which is comparable to the half-life of 10 mg/kg of infliximab in humans of 13.9 days (335.1 hr).[21] Approximately 90% of XTMAB-16 after a single dosing is expected to be eliminated from the system in 8 weeks. Therefore, the 8-week study duration is considered adequate to support safety and PK, biomarker, and immunogenicity analyses.

In support of the effect of XTMAB-16 on TNFα, additional biomarkers associated with TNFα activity and sarcoidosis have been selected for investigation in this first-in-human (FIH) study. The biomarkers selected for this study are sIL-2R, ACE, TNFα, and IL-6. ACE is a common biomarker used in the diagnosis of sarcoidosis.[43] sIL-2R is a surrogate marker for T cell activation, is significantly elevated in sarcoidosis patients, and has been shown to have a high and superior sensitivity and specificity, compared to ACE, for diagnosing sarcoidosis in patients.[13] IL-6 is elevated in patients with sarcoidosis and may be involved in the initiation and maintenance of alveolitis by activating and causing the proliferation of T cells.[36] TNFα induces IL-6 through the nuclear factor k B pathway and, thus, inhibition of TNFα through XTMAB-16 is likely to be reflected in a change in IL-6 circulating levels.[25] These biomarkers are normally low or undetectable in healthy participants. However, as XTMAB-16 is intended for use in patients with pulmonary sarcoidosis (in whom these biomarkers are likely to be elevated), XTMAB-16 is expected to influence the levels of these biomarkers in patients. Measuring these biomarkers in healthy participants will establish relative baseline levels of these biomarkers for comparison in later trials in patients.

4.3 JUSTIFICATION FOR DOSE

The participants in this study will receive a single IV infusion of placebo or 2 or 4 mg/kg of XTMAB-16 in 250 mL of 0.9% Sodium Chloride Injection, US Pharmacopeia (USP).

[redacted]

Based on the clinical data from literature in sarcoidosis patients with pulmonary involvement, and safety data from the mouse toxicology study, the low doses of 2 to 4 mg/kg of XTMAB-16 in the current study are considered safe and expected to be relevant for PK and efficacy biomarker analyses to support further clinical development. Using mg/kg scaling from the 40 mg/kg TgTC mouse NOAEL in the 13-wk toxicology study, the 2 and 4 mg/kg human dose cohorts provide a 5 and 10-fold safety margin respectively.

Projected human safety margins were calculated by comparing the NOAEL exposure in the toxicology species (TgTC mice dosed at 40 mg/kg) to the projected clinical exposures. Using TK data generated from the 6-week GLP toxicology study in TgTC mice, a 2-compartmental model with first order absorption and elimination using a mixed ratio error model was developed for XT-MAB16. The model was allometrically scaled to humans using published allometric exponents. The allometrically scaled human model was then used to simulate the planned FIH doses for XTMAB-16 for a 70 kg human (Table 3).

The projected human doses were then compared to the calculated C_{max} and $AUC_{0-\infty}$ from the 13-week NOAEL to generate exposure based safety margins (Table 3). Using a model built from

the 6-week toxicology study Comparing the $AUC_{0-\infty}$ (624865.9 hr•mg/mL) of the 40 mg/kg group dosed with XT-MAB16 in TgTC model toxicology study to the estimated $AUC_{0-\infty}$ of the 2 mg/kg dose in humans (14000 hr•mg/mL) the safety margin for the starting dose is approximately 89-fold. Comparing the C_{max} (1104.9 mg/mL) of 40 mg/kg dose of XTMAB-16 in TgTC to the estimated C_{max} (47.8 mg/mL) of 2 mg/kg dose in humans, the safety margin for the starting dose is approximately 23-fold.

In the repeat-dose 13-week toxicology study, the animals received 7 biweekly IV injections (Day 1, 15 and 29), while in the current study, only a single IV infusion will be administered to the human subjects.

Therefore, the single administered doses of 2 and 4 mg/kg in the planned FIH study are considered scientifically reasonable and meet current guidance for Maximum Safe Starting Dose 2005 and appropriate safety margins for both the starting and highest dose based on the NOAEL exposure reported in the 13-week GLP TgTC toxicology study.

The relevant human projected safety margins calculated from the 13-week toxicology study are summarized in Table 3 below.

Table 3 Allometrically Scaled Estimated Human PK Parameters

PK Parameter	2 mg/kg	4 mg/kg
C_{max} (µg/mL) Mean	47.8	95.7
Safety Margin for C_{max}	23	12
$AUC_{0-\infty}$ (µg/mL•hr) Mean	14000	28000
Safety margin for $AUC_{0-\infty}$	45	22

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit shown in the Schedule of Assessments (SoA), Section 1.3.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Participants must meet all of the following criteria to be eligible for participation in this study:

1. In the opinion of the Investigator, the participant is capable of understanding and complying with protocol requirements.
2. The participant is willing to sign and date a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures, including requesting that a participant fast for any laboratory evaluations.
3. The participant is a healthy adult male or female aged 18 to 45 years, inclusive, at the time of informed consent.
4. The participant weighs between 45 kg (99 lbs) and 100 kg (220 lbs) and has a body mass index (BMI) between 18.0 and 30.0 kg/m^2, inclusive, at the time of informed consent.
5. The participant has physical examination, clinical laboratory values, and ECG results that are clinically acceptable. Laboratory results outside of the reference range must be documented as acceptable by the Investigator and Sponsor.
6. A male participant who is nonsterilized and sexually active with a female partner of childbearing potential must agree to use highly effective contraception from the time of signing the informed consent throughout the duration of the study, and for 90 days after the last dose of study drug. See Appendix 3 for details on contraception requirements during the study.
7. A female participant of childbearing potential who is sexually active with a nonsterilized male partner agrees to routinely use highly effective contraception from the time of signing the informed consent, throughout the duration of the study, and for 90 days after the last dose of study drug. See Appendix 3 for details on contraception requirements during the study.

5.2 EXCLUSION CRITERIA

Participants who meet any of the following exclusion criteria will not be eligible for participation in this study:

1. The participant has received any investigational compound within 90 days before dosing.
2. The participant is an immediate family member, CRU employee, or is in a dependent relationship with a CRU employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.

3. The participant has any clinically significant illness, such as cardiovascular, neurologic, pulmonary, hepatic, renal, metabolic, gastrointestinal, urologic, immunologic, endocrine, or psychiatric disease or disorder, or other abnormality, which may affect the participant's safety, increase risk of seizure or lower the seizure threshold, or potentially confound the study results. It is the responsibility of the Investigator to assess the clinical significance of any conditions the participant may have; however, consultation with the Xentria Medical Monitor may be warranted.
4. The participant has a known hypersensitivity to any component of the formulation of XTMAB-16.
5. The participant has a positive result for drugs of abuse (defined as any illicit drug use) or alcohol at Screening or Baseline (Day -2).
6. The participant has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 1 year prior to Screening or is unwilling to agree to abstain from alcohol and drugs throughout the study.
7. The participant has taken any excluded medication, supplements, or food products during the time periods listed in Table 4.
8. If female, the participant is pregnant or lactating or intends to become pregnant before, during, or within 90 days after the last dose of study drug or intending to donate ova during such time period.
9. If male, the participant intends to donate sperm during the study or within 90 days after the last dose of study drug.
10. The participant has a history of autoimmune disease or respiratory disorders.
11. The participant or any immediate family member has a history of cancer, except basal cell carcinoma, that has not been in remission for at least 5 years prior to Baseline (Day -2).
12. The participant has a condition that can potentially reduce drug clearance (eg, renal or hepatic insufficiency).
    a. Glomerular filtration rate <60
    b. ALT >41 U/L
    c. AST > 34 U/L
    d. Alkaline phosphatase >117 U/L
    e. Total protein >8.2 g/dL
    f. Total bilirubin >11.9 mg/dL
    g. Gamma glutamyl transferase >43 U/L (female), >73 U/L (male)

h. Lactate dehydrogenase >246 U/L (female) or >241 (male)

i. Prothrombin time >14.6 seconds

13. The participant has current or recent (within 6 months) circulatory or hematologic disease that would be expected to influence the absorption of drugs (ie, a history of malabsorption, distribution, or clearance of investigational product).
14. The participant has a positive test result for hepatitis B surface antigen (HBsAg), hepatitis B core antigen antibody, hepatitis C virus (HCV) antibody, COVID-19, TB, or a known history of human immunodeficiency virus (HIV) infection at Screening.
15. The participant has used nicotine-containing products (including but not limited to cigarettes, pipes, cigars, chewing tobacco, nicotine patch, or nicotine gum) within 28 days prior to Baseline. Cotinine test is positive at Screening or Baseline.
16. The participant has poor peripheral venous access.
17. The participant has donated or lost 450 mL or more of his or her blood volume (including plasmapheresis) or had a transfusion of any blood product within 90 days prior to dosing.
18. The participant has a Screening or Baseline abnormal, clinically significant ECG. Entry of any participant with an abnormal, not clinically significant ECG must be approved and documented by signature of the PI or medically qualified sub-Investigator. In the case of a QTcF interval >450 ms (men) or >470 ms (women; participants with bundle branch block) or PR outside the range of 120 to 220 ms, the assessment may be repeated once at the Screening Visit or Baseline for eligibility determination.
19. The participant has a supine blood pressure outside the ranges of 90 to 140 mm Hg for systolic and 50 to 90 mm Hg for diastolic. The assessment may be repeated once for eligibility determination at the Screening Visit or Baseline.
20. The participant has a resting pulse outside the range of 50 to 90 bpm (not on ECGs). The assessment may be repeated once for eligibility determination at the Screening Visit or Baseline.
21. The participant has abnormal Screening or Baseline laboratory values that suggest a clinically significant underlying disease or the participant has the following laboratory abnormalities: ALT >41 U/L and/or AST > 34 U/L.

5.3 LIFESTYLE CONSIDERATIONS

From Day -2 and throughout the study duration, participants should refrain from excessive use of alcohol, tea, coffee, chocolate, quinine, or caffeine-containing beverages.

Participants will be requested to follow a stable lifestyle with no intensive physical activity from Day -2 through the end of study (EOS) visit.

During the confinement, standardized breakfast when applicable, lunch, and dinner will be given as scheduled by the CRU, with every participant on the same meal schedule. There will be no water restrictions for participants; water supply will be at least 1500 mL for each 24-hour period. During the confinement period (Day -2 to Day 8), participants will be given a menu for the dosing period that includes 3 meals and an evening snack, not to exceed 30% fat (relative to the total calories). The meals served on the PK assessment days should be identical for each cohort in the study. The study menu should be recorded and submitted to the study file with a copy provided to the Sponsor prior to the start of the study. Whether the meal was fully consumed, or not, will be recorded.

If a blood draw or any study procedure coincides with a meal, the blood draw will take precedence followed by the study procedure and then the meal.

XTMAB-16 and placebo will be administered on Day 1 in same manner for each cohort (pre- or post-meal). Participants may consume water ad libitum following dosing.

Vital signs will be collected in a supine position except for during the infusion, when the procedures will be performed in a semi-supine/semi-reclined position (see Section 8.2.3). Infusion will occur in a semi-supine/semi-reclined position. After dosing, the participant will be observed by staff for up to 2 hours—at the Investigator's discretion for up to 4 hours, if necessary – except as necessitated by the occurrence of an AE or study procedures (eg, obtaining 12-lead ECG).

Participants will be immunocompromised by administration of study treatment and should be instructed to quarantine at home for 6 days after discharge from the study unit.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a nonclinically significant laboratory abnormality may be rescreened once at the discretion of the Investigator. Rescreened participants should be assigned the same participant number as for the initial screening; those who fail the drug test may not be rescreened.

5.5 REPLACEMENT OF PARTICIPANTS

- Participants who sign the informed consent form and are randomized but do not receive the study intervention may be replaced.

- Participants who sign the informed consent form, are randomly assigned to treatment, receive the study intervention, and subsequently withdraw or are withdrawn or discontinued from the study before Week 2, will be replaced.
- Participants who are lost-to-follow-up will be replaced.

Replacement participants will be assigned to the same treatment assignment as the participant who discontinued.

6 STUDY INTERVENTION

6.1 STUDY DRUG ADMINISTRATION

6.1.1 STUDY DRUG DESCRIPTION

[redacted]

Characterization studies were performed on XTMAB-16 drug substance batches produced in the commercial scale. Results include testing of chemical, physical, and biological properties to establish specifications in terms of identity, purity, and biological activity by a panel of orthogonal assays.

Nonclinical studies of in-vitro biological activity of XTMAB-16 have been performed, including a potency assay, ligand binding assays to TNFα, tissue cross-reactivity, antibody-dependent cellular cytotoxicity, and complement-dependent cytotoxicity activity, and binding to Fc receptors. Please refer to the IB for details.

6.1.2 DOSING AND ADMINISTRATION

XTMAB-16 or placebo will be administered once on Day 1 by IV infusion at the required concentration in a volume outlined in the Pharmacy Manual over a period of not less than 2 hours (unless otherwise specified in the Pharmacy Manual). The dose to be administered (0 [placebo], 2, or 4mg/kg) will be determined by the participant's cohort and treatment assignment.

Before XTMAB-16 infusion, the Investigator should carefully read the pretreatment checklist and go over the questions with the participant. Refer to the Administration Guide for the supplies needed, administration instructions, and important information on what to do in the event the participant experiences an infusion reaction.

XTMAB-16 should be administered with an infusion kit and 1.2 micron filter via an infusion pump. See the Pharmacy Manual for details.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The Sponsor will notify the Investigator and pharmacy prior to shipment of drug supplies and other related clinical supplies regarding the anticipated date of their arrival at the pharmacy. Shipment will be sent directly to the delegated personnel at the pharmacy.

All shipped clinical supplies will be appropriately documented to ensure proper handling in case of emergency.

Shipment will be sent under controlled conditions. Each shipment of clinical supplies for the trial will contain a certificate of analysis and a shipment certificate detailing the content of shipment.

Transportation temperature will be monitored and recorded by temperature-monitoring devices. The CRU is required to acknowledge receipt of the study drug and verify the contents, quality, and temperature of the study drug.

Initial clinical supply shipment will be sent automatically upon regulatory and Sponsor approval.

XTMAB-16 must be kept in a secured area with access limited to designated study personnel. Only personnel under the supervision of either the Investigator or the local pharmacist are authorized to handle XTMAB-16.

Refer to the Pharmacy Manual for additional information and details.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

[redacted] This information is also detailed in the pharmacy manual.

The matching placebo has the same formulation as that the drug product except contains no XTMAB-16. [redacted]

The study drug and matching placebo will be packaged and labeled according to the current Good Manufacturing Practice (cGMP) guidelines for drugs used in clinical trials and any other

relevant local regulatory requirements. Details of the packaging and labeling will be found in the Pharmacy Manual provided by the Sponsor and/or delegate.

6.2.3 PRODUCT STORAGE AND STABILITY

XTMAB-16 drug product should be stored at 2°C to 8°C (refrigerate). The clinical supplies storage area at the CRU must be monitored by the CRU staff for temperature consistency with the above instructions. Documentation of temperature monitoring should be maintained at all times until study closure.

Do not use beyond the expiry date provided by the Sponsor.

Upon removal from refrigerated storage, XTMAB-16 cannot be returned to refrigerated storage. XTMAB-16 vials are for single use only. Any unused portion should be placed in quarantine for monitor review. No vials should be discarded without Sponsor approval.

Infusion should begin within 1.5 hours of reconstitution and dilution. The infusion must be administered over a period of not less than 2 hours and must use an infusion set with an inline, sterile, non-pyrogenic, low-protein-binding filter (pore size of 1.2 µm or less). The vials do not contain antibacterial preservatives; therefore, any unused portion of the infusion solution should not be stored for reuse.

The Investigator will be notified of any expiry date or retest date extension of Sponsor-supplied drug during the study conduct. On expiry date notification from the Sponsor or designee, the CRU must complete all instructions outlined in the notification, including segregation of expired Sponsor-supplied drug for destruction.

In the event of expiry date extension of supplies already at the CRU, a memo will be provided by the Sponsor with the retest period and retest date.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

In this study participants will be randomly assigned to treatment (XTMAB-16 or placebo) and treatment assignment will be double-blind: participants and all study staff will be blind to participant treatment assignment for the duration of the study except as specified.

The randomization schedule will be generated by an unblinded statistician (third-party unblinded) and will be provided to the CRU pharmacist prior to the start of this study. All randomization information will be stored in a secured area, accessible only by authorized personnel.

The Investigator (or designee) will assign participant numbers as participants are screened for the study. In accordance with the randomization numbers, the participant will receive the study treatment regimen assigned to the corresponding randomization number.

To maintain the treatment blind, an otherwise uninvolved, third-party unblinded CRU staff member (eg, pharmacist) will be responsible for the preparation and dispensing of all study

treatment according to the randomization schedule and assigned treatment for the individual participant. The unblinded pharmacist will have no contact with study participants and will ensure that no treatment assignment information is transmitted to study unit staff except as defined in Section 6.3.1.

6.3.1 UNBLINDING PROCEDURE

The study drug blind shall not be broken by the Investigator unless information concerning the treatment assignment is necessary for the medical treatment of the participant. All study assessments and causality should be performed, if possible, prior to unblinding. In the event of a medical emergency, if possible, the Sponsor's Medical Monitor should be contacted before the treatment assignment blind is broken to discuss the need for unblinding.

For unblinding a participant, the treatment assignment blind can be obtained by contacting the dispensing pharmacist. Code break envelopes will be supplied for emergency unblinding when the pharmacist is unavailable.

The Sponsor must be notified as soon as possible if the treatment assignment blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents and the same information (except the time) must be recorded on the electronic case report form (eCRF).

If the blind must be broken for the safety of the participant, the PI and CRO should refer to the Unblinding Plan for instructions and details for review of safety data for that cohort and the impact on dose escalation and/or stopping rules.

If any CRU personnel are unblinded, study drug dosing must be stopped immediately and the participant must be withdrawn from the study.

No change should be made to any assessment of the participant after unblinding.

6.3.2 PREPARATION

Reconstitute each XTMAB-16 or placebo vial with 10 mL of sterile WFI, USP, using a syringe equipped with a 21-gauge or smaller needle. Remove the flip-top from the vial and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center of the rubber stopper and direct the stream of sterile WFI, USP, to the glass wall of the vial. Gently swirl the solution by rotating the vial to dissolve the lyophilized powder. Avoid prolonged or vigorous agitation. DO NOT SHAKE. Foaming of the solution on reconstitution may occur and is not unusual. Allow the reconstituted solution to stand at room temperature for 5 minutes. The solution should be colorless to pale-yellow and opalescent and may develop a few translucent particles, as XTMAB-16 is a protein. Do not use if opaque particles, discoloration, or other foreign, particles are present.

Please refer to additional instructions in the Pharmacy Manual.

The study drug will be prepared by a trained, unblinded CRU staff member using aseptic technique (eg, Pharmacist). Study drug will be prepared based on the treatment assignment. The Sponsor, Investigator, study center staff, and participants will be blinded to treatment assignment and only the unblinded pharmacist or designee will be aware of the treatment assignment.

Dose preparation records will be completed and securely maintained by the dose preparer. Both XTMAB-16 and placebo have the same appearance after reconstitution and dilution, thereby ensuring that the CRU staff administering the study drug will remain blinded to treatment assignment. Details of the preparation of XTMAB-16 and placebo will be provided in the Laboratory Manual.

6.4 STUDY DRUG COMPLIANCE

All doses of study drug in this study will be administered by CRU personnel. As such, no measures of study drug compliance are included for this study beyond study drug accountability, as previously described.

If study drug administration is interrupted or stopped, the estimated total amount (percentage) of the study drug successfully administered will be recorded in the eCRF.

6.5 CONCOMITANT THERAPY

Otherwise, the use of concomitant medication should not be allowed during the study unless specified in the inclusion criteria or study procedures. However, if a concomitant medication is required for any reason, the name of the medication, indication, dose, and duration of use will be recorded on the eCRF. The Sponsor must be informed within 48 hours via email or by telephone.

Use of the agents in Table 4 (prescription or nonprescription) is prohibited from the time points specified until participant is discharged from the unit.

Table 4 Prohibited Medications and Dietary Products

28 days prior to Baseline (Day -2)	7 days prior to Baseline (Day -2)	72 hours prior to Baseline (Day-2)
Prescription medications[a]	OTC medications[b]	Poppy seeds
Nutraceuticals (eg, St. John's wort, ginseng, kava kava, ginkgo biloba, Chinese herbs, and melatonin)	Vitamin supplements[b]	
Immunization/Vaccines[c]	Alcohol containing products[b]	
Nicotine-containing products		

Abbreviations: OTC=over-the-counter.
Note: Medications noted in this table are prohibited from the time noted in the table through discharge from the CRU (Day 8), unless otherwise specified.

a Contraceptives and short-term antibiotics are allowed. Any other prescription medications are prohibited in this study.

b Occasional use of acetaminophen/paracetamol (≤1 g/day) or other medication or vitamins as approved by Xentria on a case-by-case basis is allowed. Prohibition and approval on case-by-case basis may both be acceptableterms.

c Inclusive of but not limited to H1N1 and other flu vaccinations, hepatitis, and HPV. For COVID-19 vaccinations, the final vaccination must be received no less than 30 days prior to dosing. Participants who wish to receive the COVID-19 vaccine after study drug (XTMAB-16 or placebo) dosing may do so **after Week 4 PK sampling and other assessments** have been completed.

6.5.1 RESCUE MEDICINE

Treatment for injection site reactions, hypersensitivity reactions, and/or anaphylaxis may be given, if needed. Qualified personnel and appropriate medication(s) should be available during all infusions to treat potential hypersensitivity and anaphylactic reactions. Toxicity grading of injection site reactions and vital signs changes are listed in Appendix 4. Guidelines for diagnosis and treatment for anaphylaxis are provided in Appendix 5. Please refer to Section 4.1.2.1 and Section 7.1 for the handling of participants whose infusion was prematurely terminated.

6.6 OVERDOSE

An overdose is defined as a known, deliberate, or accidental administration of study drug, to or by a study participant, at a dose above that which is assigned to that participant according to the study randomization schedule.

In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

Cases of overdose without manifested signs or symptoms will not be considered AEs. Adverse events associated with an overdose will be documented according to Section 8.6.

SAEs associated with overdose will be reported according to the procedure outlined in Section 8.6.5.

All cases of overdose (with or without associated AEs) will be collected on the eCRF.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY DRUG

A single dose of study treatment will be administered in this study. Study treatment will only be discontinued if an unforeseen occurrence interrupts or prematurely stops the 2-hr IV infusion. Discontinuation from study treatment does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from Baseline) after enrollment, the Investigator or qualified designee will determine if any change in participant management is needed. All events or clinically relevant findings that cause the interruption or premature cessation of dosing will be reported as an AE.

The data to be collected at the time of study treatment interruption or discontinuation will include the following:

- Reason dosing was interrupted/stopped
- Estimate of how much of the study treatment dose was delivered (%)
- How long the participant was observed for safety after the event
- Whether the participant continued in the study or was withdrawn.

Participants who are withdrawn from the study after interruption or premature discontinuation of study treatment dosing should undergo EOS procedures as noted in the SoA (Section 1.3).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants may withdraw from the study at any time and for any reason. The reason for participant discontinuation or withdrawal from the study will be recorded on the eCRF.

Participants may be discontinued from the study for any of the following reasons:

- Lost-to-follow-up
- Study termination by the Sponsor

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 2 consecutively scheduled visits and is unable to be contacted by the CRU staff or fails to return for the Day 71 visit.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The CRU will attempt to contact the participant and reschedule the missed visit within 7 days and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

There are no efficacy assessments for this Phase 1, FIH, clinical study.

8.2 SAFETY AND OTHER ASSESSMENTS

Planned time points for all safety and other assessments are provided in the SoA (see Section 1.3).

8.2.1 PHYSICAL EXAMINATION

- A complete physical examination will include assessments of general appearance, skin; head/neck; pulmonary, cardiovascular, gastrointestinal, external genitourinary (optional), lymphatic, and musculoskeletal systems; extremities; eyes (inspection and vision control); ears, nose; throat; and neurologic status.
- An abbreviated physical examination will include assessments of general appearance; head, ears, eyes, nose, and throat; cardiovascular; respiratory; and gastrointestinal systems (including the abdomen).
- A targeted physical examination may be conducted at any time at the Investigator's discretion and should be limited to systems of clinical relevance (ie, cardiovascular, respiratory, lymph nodes, liver.)

8.2.2 HEIGHT AND WEIGHT

Height (cm) will be measured only at Screening. Weight will be measured in kilograms according to the SoA (Section 1.3).

8.2.3 VITAL SIGNS

Oral, tympanic or temporal body temperature, respiratory rate, pulse, and systolic and diastolic blood pressure will be assessed. The method of body temperature assessment chosen should be recorded and consistent throughout the study.

If oral temperatures (°C) are taken, participants will have had no food or liquid for at least 5 minutes before assessment.

During the infusion, systolic/diastolic blood pressure and pulse should be measured in a semi-spine/semi-reclined position. For all other readings, blood pressure and pulse will be taken in a supine position after 10 to 15 minutes rest.

Respiratory rate (breaths/min) will be taken after at least 5 minutes rest; breaths are counted for 30 seconds and multiplied by 2. Respiration rate will be taken concurrently with all ECGs. During the infusion, respiration rate will be taken in a semi-supine/semi-reclined position.

8.2.4 ELECTROCARDIOGRAMS

Participants will undergo telemetry beginning on Day -1 through 50 hours after the start of infusion (Table 8). Five-minute telemetry data extraction periods should begin after 10 minutes of rest in a semi-reclined position, and when applicable, at least 15 minutes prior to the nominal PK/ADA/nAb blood collection time point and to allow completion of the ECGs prior to collection of PK/ADA/nAb sample.

Standard 12-lead ECGs will be recorded after the participant has been resting at least 10 minutes using a CAM-14 module. Single ECGs will be collected at the time points noted in the SoA (Section 1.3). Additional ECGs will be performed at the discretion of the Investigator.

Telemetry and ECG readings will be performed in a supine position after the allotted time specified above. During the infusion, procedures will be performed in a semi-supine/semi-reclined position.

The Investigator will be responsible for reviewing the ECG to assess whether the ECG is within the reference limits and to determine clinical significance of the results. If necessary, the Investigator has the right to override the interpretation and intervals as measured by the ECG machine. The ECG will be assessed for the following measures: P wave, QRS complex, U wave, QRS duration, QT interval, QTcF, T wave, ST segment, RR interval, PR interval, and qualitative results.

8.2.5 CLINICAL LABORATORY EVALUATIONS

Clinical laboratory assessments will be collected under appropriate conditions defined by the clinical unit's standard of practice.

- The research laboratory unit will be used to perform all clinical laboratory tests including serum pregnancy test, which will be assessed by the CRU staff. The Investigator should take immediate action for any safety concerns based on laboratory results.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with an underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study, including the participant's last EOS visit, should be repeated until the values return to normal or Baseline or are no longer considered clinically significant or follow-up is no longer needed per the judgment of the Investigator or Medical Monitor.
    - If such values do not return to normal/Baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 1, must be conducted in accordance with the Laboratory Manual and the SoA (Section 1.3).

Blood volumes for laboratory samples will be included in the Laboratory Manual.

8.3 PHARMACOKINETICS

Whole blood samples will be collected for measurement of serum concentrations of XTMAB-16 (Table 8). Instructions for the collection and handling of biological samples will be provided by the Sponsor in a separate Laboratory Manual. The actual date and time (24-hour clock) of each sample will be recorded in the eCRF. Samples will be used to evaluate the serum concentration and PK of XTMAB-16. Each serum sample will be divided into 2 aliquots (1 each for primary and back-up).

Measurement of concentrations of XTMAB-16 will be performed using a validated assay method by or under the supervision of the Sponsor. The analytical methods used to measure concentrations of XTMAB-16 will be described in a separate bioanalytical report. Only samples that are within the window of sample stability will be analyzed.

While PK samples must be collected from participants assigned to the placebo arm to maintain the blinding of treatment assignment, PK assay results for these participants are not needed for the safety conduct or proper interpretation of this trial and most samples will therefore not be analyzed. Personnel responsible for performing PK assays will be unblinded to participants' treatment assignments to identify appropriate PK samples to be analyzed. Samples from participants assigned to placebo may be analyzed upon request (ie, to evaluate a possible error in dosing).

Blood samples for PK/ADA/nAb will be collected for analysis from participants who experience an SAE that is also considered related to study treatment. If an SAE occurs prior to the validation of the XTMAB-16-specific PK assay, blood samples in these potential cases will be analyzed using the infliximab assay, as needed, on an individual basis. These samples from these participants will be re-analyzed as part of the batch analyses using the validated XTMAB-16-specific assay prior to completion of the study.

Blood volumes for PK samples will be included in the Laboratory Manual.

Table 5 List of Pharmacokinetic Parameters and Definitions

Parameters	Definition/Calculation
C_{max}	Maximum observed serum concentration
C_T	Serum concentration observed at the end of drug infusion, where T is the duration of infusion time
t_{max}	First time to reach C_{max} after drug administration
AUC_{0-t}	Area under the serum concentration versus time curve from time zero to the last quantifiable time point at t
$AUC_{0-\infty}$	Area under the serum concentration versus time curve extrapolated to infinity according to the following equation: $AUC_{0-\infty} = AUC_{0-t} + C_t / \lambda_z$ Values with a percentage of extrapolation >20% of $AUC_{0-\infty}$ will not be considered in the descriptive statistics
λ_z	Terminal elimination rate constant (see $t_{1/2}$ below)
$t_{1/2}$	Terminal half-life associated with the terminal phase determined according to the following equation: $t_{1/2} = 0.693/\lambda_z$ where λz is the slope of the regression line of the terminal phase of the serum concentration versus time curve, in semi-logarithmic scale. λz will be calculated by taking the regression of at least 3 points.
CL	Total body clearance of a drug from the serum calculated using the following equation: $CL = Dose / AUC_{0-\infty}$
MRT	Mean residence time of the drug in the body calculated as: $MRT = AUMC_{0-\infty} / AUC_{0-\infty}$ where $AUMC_{0-\infty}$ is area under the serum concentration moment ($C \cdot t$) versus time curve extrapolated to infinity according to the following equation: $AUMC_{0-\infty} = AUMC_{0-t} + (C_t \cdot t / \lambda_z + C_t / \lambda_z^2)$
V_z	Volume of distribution during the terminal phase calculated using the following equation: $V_z = Dose/(\lambda_z \cdot AUC_{0-\infty})$
V_{ss}	Steady state volume of distribution following IV dosing calculated as: $V_{ss} = MRT \bullet CL$

8.4 IMMUNOGENICITY

Antibodies to XTMAB-16 will be evaluated in serum samples collected from all participants according to Table 8. Additionally, serum samples should also be collected at the final visit from participants who discontinue from the study. Instructions for the collection and handling of biological samples will be provided by the Sponsor in a separate Laboratory Manual. These samples will be tested by the Sponsor or Sponsor's designee. Each serum sample will be divided into 2 aliquots (1 each for primary and a back-up).

Serum samples will be tested in a multi-tiered approach. A validated screening assay for antibodies binding to XTMAB-16 will be initially used to assess serum samples. Samples that are determined putative positive in the screening assay will then be subjected to a confirmatory assay to demonstrate that antibodies are specific to XTMAB-16. Samples that are identified as positive in the confirmatory assay will be further characterized in a validated tier assay and titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to study treatment and/or to further characterize the immunogenicity of study treatment. Serum samples will be screened for antibodies binding to XTMAB-16 and the titer of confirmed positive samples will be reported.

The detection and characterization of antibodies to XTMAB-16 will be performed using a validated assay method by or under the supervision of the Sponsor. The analytical methods used to measure immunogenicity will be described in a separate bioanalytical report. Only samples which are within the window of sample stability will be analyzed.

Samples that are confirmed positive for antibodies binding to XTMAB-16 may be further evaluated for their ability to neutralize the activity of the study treatment using a validated assay method.

Blood samples for PK/ADA/nAb will be collected for analysis from participants who experience an SAE that is also considered related to study treatment.

Blood volumes for ADA/nAB samples will be included in the Laboratory Manual.

8.5 BIOMARKERS

Whole blood samples will be collected for measurement of exploratory circulating biomarkers according to Table 8 and serum will be used for analysis. Circulating biomarkers that will be evaluated include ACE, sIL-2R, IL-6, and sTNFα.

Instructions for the collection and handling of biological samples will be provided by the Sponsor in a separate Laboratory Manual. The actual date and time (24-hour clock time) of each sample will be recorded in the eCRF. Data collected from analyses of circulating biomarkers may be used to correlate exposure to safety or other parameters or after the study.

Measurement of circulating biomarkers will be performed using a fit-for-purpose qualified assay method. The analytical methods used to measure these biomarker endpoints will be

described in separate bioanalytical reports. Only samples that are within the window of sample stability will be analyzed.

Blood collection volumes for biomarker samples will be included in the Laboratory Manual.

8.6 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.6.1 DEFINITION OF ADVERSE EVENTS

An AE is any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

8.6.2 DEFINITION OF SERIOUS ADVERSE EVENTS

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- Life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.6.3 CLASSIFICATION OF AN ADVERSE EVENT

8.6.3.1 SEVERITY OF EVENT

The Investigator will make an assessment of severity for each AE and SAE reported during the study and assign it to 1 of the following categories:

Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.

Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.6.3.2 RELATIONSHIP TO STUDY INTERVENTION

All AEs must have their relationship to the study drug assessed by the Investigator who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study drug must always be suspect.

- **Related** – The AE is known to occur with the study drug, there is a reasonable possibility that the study drug caused the AE, or there is a temporal relationship between the study drug administration and the event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study drug and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study drug caused the event, there is no temporal relationship between the study drug and event onset, or an alternate etiology has been established.

8.6.3.3 EXPECTEDNESS

The Investigator will be responsible for determining whether an AE is expected or unexpected. XTMAB-16 has not previously been administered in humans. [redacted]

8.6.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of CRU personnel during study visits and interviews of a participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate eCRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as Baseline and not reported as an AE. However, if the participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The Investigator or designee will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for nonserious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the Investigator will inquire about the occurrence of AE/SAEs since the last visit. vents will be followed for outcome information until resolution or stabilization.

8.6.5 SERIOUS ADVERSE EVENT REPORTING

The PI or designee is responsible for providing notification to the Sponsor of any SAE, whether deemed study drug-related or not, that a participant experiences during the study within 24 hours of becoming aware of the event.

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

- Study number
- Participant number
- Sex
- Date of birth
- Name of PI and full CRU address
- Details of SAE
- Criterion for classification as 'serious'
- The study drug name, or code if unblinded, and treatment start date
- Date of SAE onset
- Causality assessment (if sufficient information is available to make this classification)

All SAEs will be followed until satisfactory resolution, until the Investigator deems the event to be chronic, or the participant is stable. Other supporting documentation of the event may be requested by Parexel Safety Services/Sponsor and should be provided as soon as possible.

The SAE form will be sent to:

Parexel Safety Services
Email: [redacted]
FAX: [redacted]

The Sponsor will be responsible for notifying regulatory authorities (eg, FDA, EMA, as applicable) of any unexpected fatal or life-threatening suspected adverse reaction, suspected unexpected serious adverse reaction (SUSAR), or other applicable SAE as soon as possible, but in no case later than 7 calendar days after the Sponsor's initial receipt of the information. In addition, the Sponsor must notify regulatory authorities and all participating Investigators in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the Sponsor determines that the information qualifies for reporting.

The Sponsor will notify the Investigator of relevant information about SUSARs that could adversely affect the safety of participants in a timely fashion. Follow-up information may be submitted if necessary. The Sponsor will also provide annual safety reports for submission to the regulatory authority and the IRB/IEC responsible for the clinical study. These updates will include information on SUSARs and other relevant safety findings.

8.6.6 EVENTS OF SPECIAL INTEREST

Based on clinical data from the TNFα inhibitor package inserts and nonclinical data to date for XTMAB-16, the adverse event of special interest (AESI) for this study is:

- Anaphylactic shock

AESIs will be reported using the appropriate eCRF. In addition, AESIs that are also SAEs will be reported using the SAE form and sent to Parexel Safety Services (see Section 8.6.5).

8.6.7 REPORTING OF PREGNANCY

- The Investigator will collect pregnancy information on any female participant or female partner of a male participant who becomes pregnant while the participant is in this study.
- If a pregnancy is reported, the Investigator should inform Parexel Safety Services within 24 hours of learning of the pregnancy using the SAE Form.
- If a pregnancy occurs, the participant will be followed to determine the outcome of the pregnancy, but no longer than 6-8 weeks after the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Pregnancy is not considered an SAE but should be reported in the eCRF and on the Pregnancy Form in accordance with SAE reporting timelines as per Section 8.6.5. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.
- Any post-study pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor as per Section 8.6.5. While

the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

8.7 UNANTICIPATED PROBLEMS

8.7.1 DEFINITION OF UNANTICIPATED PROBLEMS

The Office for Human Research Protections (OHRP) considers unanticipated problems (UPs) involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent form (ICF); and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Investigators should refer to the Remicade (infliximab) package insert for known risks and AEs with the use of this class of drug (TNFα blockers).[32]

8.7.2 UNANTICIPATED PROBLEM REPORTING

The Investigator will report UPs to the IRB and to Parexel Safety Services. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number.
- A detailed description of the event, incident, experience, or outcome.
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP.
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the Parexel Safety Services within 24 hours of the Investigator becoming aware of the event.

- Any other UP will be reported to the IRB and to the Parexel Safety Services within 7 days of the Investigator becoming aware of the problem.

All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the OHRP within 7 days of the IRB's receipt of the report of the problem from the Investigator.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Hypothesis testing will not be conducted for this study.

9.2 SAMPLE SIZE DETERMINATION

The selection of 24 participants (12 per cohort) was based on feasibility and precision around the estimates for target variables associated with the primary and secondary endpoints. No sample size calculation was performed.

9.3 POPULATIONS FOR ANALYSES

- **Enrolled Set (ES)**: The ES will consist of all participants who have given informed consent.
- **Full Analysis Set (FAS)**: The FAS will consist of all participants randomized into the study. Participants in this analysis set will be used for analyzing demographics and other baseline characteristics.
- **Safety Set**: The safety analysis set will consist of all participants who are randomized to treatment and have received 1 dose of study drug. Participants in this analysis set will be used for demographics, baseline characteristics, and safety summaries.
- **Pharmacokinetic Per-Protocol Set (PK-PPS)**: The PK-PPS set will consist of all participants in the Safety Set who provide at least 1 quantifiable serum XTMAB-16 PK sample postdose without important protocol deviations that would affect the concentration.
- **Biomarker Set**: The PD set will consist of all participants in the PK-PPS who have at least 1 postdose biomarker measurement.

If any participants are found to be noncompliant in dosing schedule or with incomplete data, a decision will be made on a case-by-case basis as to their inclusion in the PK and biomarker analysis sets but nevertheless will be presented in the participant listings.

9.4 STATISTICAL ANALYSES

Statistical analysis and generation of tables, figures, study participant data listings, and statistical output will be performed using SAS® Version 9.4 or higher.

All original and derived parameters will be listed and described using summary statistics. For continuous parameters, number of participants with available measurements, mean, standard deviation (SD), median, minimum, and maximum and for categorical parameters, number of participants and percentages (to 1 decimal place) in each category will be presented.

All descriptive statistics will be presented by treatment where applicable (eg, biomarkers), including columns for all treated participants and all participants on demographics, baseline characteristics, and AE displays, and using the available data for the study population as observed. Summaries of concentration data will be based on geometric mean and geometric SD instead of arithmetic versions. All tabulations will be sorted by treatment, parameter, and Day (including time relative to dosing if applicable, unless otherwise stated). Only scheduled visits and times relative to dosing will be included in the tabulation.

Categorical data will be summarized by Day/Week/Time and treatment.

9.4.1 GENERAL APPROACH

Details of the data analysis for this study will be provided in the Statistical Analysis Plan (SAP), which will be finalized prior to database lock.

Unless otherwise specified, the last value obtained prior to infusion of study medication (Day 1) will be used as the baseline value. If a baseline measurement is missing, and a screening value available, the screening value will be utilized as Baseline instead.

9.4.2 SAFETY ANALYSES

9.4.2.1 LABORATORY EVALUATIONS, VITAL SIGNS AND ECG

Laboratory evaluations, vital signs, and ECGs will be analyzed for the Safety Set for observed cases. Descriptive statistics will be presented by cohort and treatment at each time point: change from Baseline in vital signs, serum chemistry, hematology, and urinalysis. For laboratory data, changes between the Baseline or, if missing, screening value and each posttreatment assessment may be presented in shift tables or using other summaries as detailed in the SAP. Assessment of liver-related changes will include:

- 3 ×-, 5 ×-, 10 ×-, and 20 × ULN elevations of AST, ALT, and either ALT or AST
- Any elevations of bilirubin: elevated total bilirubin to >2 × ULN
- Any elevations of ALP >1.5 × ULN
- Elevation of AST or ALT (>3 × ULN) accompanied by elevated bilirubin (>1.5 × ULN, >2 × ULN)
- Elevation of AST or ALT in temporal association with nausea, vomiting, anorexia, abdominal pain, or fatigue
- Any liver-related deaths and liver-related treatment discontinuations.

For ECG parameters, descriptive analysis and shift tables from predose will be performed. Further concentration QT analysis (eg, time-matched QT, and QTc analyses for XTMAB-16 and

placebo may be evaluated, including effect of XTMAB-16 concentration on QTc, and categorical analyses) and will be defined in a finalized SAP.

9.4.2.2 ADVERSE EVENTS

Safety variables will be analyzed for all study participants in the Safety Set.

Adverse events will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 23 or higher.

The frequency of all AEs during the study will be presented for each cohort and treatment separately by SOC and PT. The data will be displayed as the number of participants experiencing the AEs, percentage of participants, and the number of events.

All TEAEs (defined as those AEs with an onset date/time on or after the start of infusion on Day 1 to end of safety follow-up), serious and nonserious, including deaths, will be tabulated and listed. Laboratory safety parameters that are reported as AEs will also be tabulated and listed.

9.4.2.3 IMMUNOGENICITY

Anti-drug antibodies and nAb at each sampling time will be summarized with descriptive statistics (N, mean, SD, coefficient of variation [CV], geometric mean, geometric CV, median, minimum, and maximum) for each dose.

If ADA or nAb are detected, a direct link model may be used to describe the relationship between the serum concentration of XTMAB-16 and ADA or nAb levels, as AUC and time point concentration measurements to explore the time-dependence.

9.4.3 PHARMACOKINETICS

The PK analysis will be conducted for patients who have sufficient plasma concentration data to facilitate the calculation of at least one PK parameter and had no important protocol deviations affecting the PK variables as confirmed during a pre-analysis review of the data before database lock. The PK parameters will be calculated from the plasma concentration-actual time profiles. The non-compartmental analysis will be performed using Phoenix® WinNonlin® Software version 8.0 or higher (Certara, LP).

9.4.3.1 SERUM CONCENTRATION-TIME DATA

Individual serum concentrations of XTMAB-16 at each PK sampling time (predose, at completion of infusion, and all other timepoints after the start of infusion) will be summarized with descriptive statistics (N, mean, SD, CV, geometric mean [gMean], geometric coefficient of variation [gCV], median, minimum, and maximum) for each dose. For descriptive statistics of the concentration-time data summaries, the nominal times (ie, planned times) will be used.

Figures for individual serum concentration of XTMAB-16 versus time profiles will be generated on regular and semi-log scales with mean for each dose. Figures for mean ±SD serum concentration of XTMAB-16 versus time profiles will be generated on regular and semi-log scales together for all doses.

9.4.3.2 PHARMACOKINETIC PARAMETERS

For determination of PK parameters, the actual sampling times (taking into account the actual dates and times) will be used. The following PK parameters will be obtained: C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, % $AUC_{0-\infty}$, CL, $t_{2/1}$, λ_z, V_z, V_{ss}, and MRT. Individual dose-normalized parameters for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ will also be summarized in terms of dose-normalized C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ ($C_{max,norm}$, $AUC_{0-t,norm}$, and $AUC_{0-\infty,norm}$, respectively). Individual PK parameters of XTMAB-16 will be summarized with descriptive statistics (N, mean, SD, CV, gMean, gCV, median, minimum, and maximum) for each dose.

Dose proportionality will be evaluated for these PK parameters, viz. C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ by the power model (PK parameter = $\alpha \bullet dose^{\beta}$). The power model will be fit on the log-transformed linear scale: log (PK parameter) = log(α) + β • log(dose). An estimate of unity for β will indicate perfect dose linearity.

Details of the PK analysis, including PK Tables, Listings, and figures, will be provided in the SAP.

9.4.4 BIOMARKER ANALYSIS

Biomarkers (ACE, sIL-2R, IL-6, and sTNFα) at each sampling time (predose, at completion of infusion, and postinfusion timepoints) will be summarized with descriptive statistics (N, mean, SD, CV, geometric mean, geometric CV, median, minimum, and maximum) for each dose. Percent change from Baseline over time and total change from Baseline will be analyzed.

Details of the biomarker analysis will be provided in the SAP.

9.4.4.1 BIOMARKER-CONCENTRATION-TIME DATA

All subjects without any major deviations related to study drug administration and for whom any biomarker (or effect) data are available will be included in the biomarker analysis. However, subjects being included in this population and having received only placebo will also be included as part of this data set.

Details of the biomarker analysis will be provided in the SAP.

9.4.4.2 PHARMACOKINETIC AND BIOMARKER RELATIONSHIP

The relationship between each biomarker concentration and XTMAB-16 concentration collected at the same time point may be graphically displayed for individual subjects, and for mean data for each dose. In addition, these figures will also be generated for each biomarker with all the data pooled across all the doses.

Details of the PK and biomarker relationship analysis will be provided in the SAP.

9.4.4.3 BIOMARKER PARAMETERS

These biomarker (or effect) parameters will be obtained, if data permit: area under the effect-time curve (AUEC), maximum observed effect ($E_{max,obs}$), and time to reach maximum observed effect ($t_{Emax,obs}$). The overall results of the biomarker assessments will determine whether these specific analyses will be performed.

If applicable, a PK/PD direct link model may be used to describe the relationship between biomarker levels and the XTMAB-16 concentrations at each time.

Details of the biomarker analysis will be provided in the SAP.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Descriptive statistics (N, mean, SD, median, minimum, and maximum) will be used to present the continuous demographic variables and baseline characteristics for each XTMAB-16 dose level, pooled placebo, and overall total. For categorical variables, the number and percentage of participants will be tabulated for each XTMAB-16 dose level, pooled placebo, and overall total. Additional details will be presented in the SAP.

9.4.6 PLANNED SAFETY REVIEW

Blinded safety data of sentinel subjects for each cohort will be reviewed by the PI as a non-comparative analysis at least 48 hours before enrollment of the remaining participants in that cohort.

9.4.7 HANDLING OF PROTOCOL DEVIATIONS

Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being. The criteria for identifying important protocol deviations will be defined within the SAP. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and data evaluation. All important deviations will be identified and documented prior to unblinding to confirm exclusion from analysis sets.

9.4.8 HANDLING OF DROPOUTS OR MISSING DATA

Missing data will not be imputed. See Section 5.5 for details on replacement of participants who discontinue prior to assessment of the primary PK endpoint.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting study intervention.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the participant's agreeing to participate in the study and continues throughout the study participation. Consent forms will be IRB-approved, and the participant will be asked to read and review the document. The Investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing.

The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records.

The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, Investigators, the IND Sponsor, and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform study participants and the IRB and the

Sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the Sponsor, IRB, and/or FDA or other regulatory authorities.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy are strictly held in trust by the participating Investigators, their staff, and the Sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the Sponsor, representatives of the IRB, regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The CRU will permit access to such records.

The study participant's contact information will be securely stored at the CRU for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for in accordance with Sponsor obligation (20 years from regulatory approval).

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the data management company responsible for data management, analysis, and reporting. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the CRU and by data management research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived by the Sponsor.

All information generated in this study must be considered highly confidential and must not be disclosed to any people not directly concerned with the study without written prior permission from the Sponsor. Authorized regulatory officials and Sponsor personnel (or their representatives) will be allowed full access to inspect and copy the records.

All study investigational product, participant bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the Sponsor. Participants will only be identified by unique subject numbers on eCRFs.

Every participant will be given a copy of each version of the form that he/she signs before and during the study. Each ICF may also include authorization allowing the institution, Investigator, and Sponsor to use and disclose personal health information in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Blood and serum specimen storage outside the study-required assessments is optional and requires participants to sign an ICF. Refusal to participate in this optional specimen storage does not affect a participant's ability to be enrolled in the study. A participant may choose to participate in this specimen storage at Screening or any time during the study, up to and including the EOS visit.

With the participant's approval, and as approved by the central IRB, de-identified biological samples will be stored at a certified, licensed central laboratory. These samples could be used to research the causes of pulmonary sarcoidosis, its complications, and other conditions for which individuals with pulmonary sarcoidosis are at increased risk, and to improve treatment. The central laboratory will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research.

Once samples have been analyzed, specimens will be destroyed. If no analyses have been completed within 5 years following EOS, samples will be destroyed.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Table 6 lists the key personnel for this study. Additional study contact information will be provided in the Study Operations Manual.

Table 6 Key Study Personnel for Protocol XTMAB-16-101

Principal Investigator	Medical Monitor	Key Sponsor Contact	Chief Medical Officer
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of the Medical Reviewer at the clinical research laboratory unit where the study is being conducted. Data will be shared with the Sponsor Medical Director, selected key medical advisors, and the study team lead for any reviews and discussions required.

10.1.7 CLINICAL MONITORING

CRU monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with ICH GCP, and with applicable regulatory requirement(s).

Monitoring for this study will be performed by a Sponsor-contracted Clinical Research Associate.

Details of CRU monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

Independent audits will be conducted by a Sponsor-designated, qualified person to ensure monitoring practices are performed and that monitors are following the CMP.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The CRU will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe the CRU quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the CRU for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors (blinded and unblinded) will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements (eg, GLP, GMP).

The investigational CRU will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the CRU under the supervision of the Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the eCRF derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a 21 CFR Part 11-compliant data capture system provided by Parexel. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study 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 until at least 2 years have elapsed since the formal

discontinuation of clinical development of the study drug. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained. Upon the request of the Sponsor, the study record may be delivered to the Sponsor from the CRO.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, ICH GCP, or Clinical Operations Plan (COP) requirements. The noncompliance may be either on the part of the participant, the Investigator, or the CRU staff. If a deviation occurs, corrective actions are to be developed by the CRU and implemented promptly.

It is the responsibility of the site Investigator to use continuous vigilance to identify and report deviations as soon as possible. All deviations must be addressed in study source documents and must be sent to the reviewing IRB per their policies. The CRU Investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the Protocol Deviation Plan, COP, Data and Medical Management Plans, blind data review documentation, and SAP.

The study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well-being of the participant requires immediate intervention, based on the judgment of the Investigator (or a responsible, appropriately trained professional designated by the Investigator). In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the Investigator or designee must contact the Medical Monitor and the Sponsor at the earliest possible time by telephone. This will allow an early joint decision regarding the participant's continuation in the study. This decision will be documented by the Investigator and the Medical Monitor.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH-funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested

from other researchers no sooner than 5 years after the completion of the primary endpoint by contacting the Sponsor.

It is understood by the Investigator that the information generated in this study will be used by the Sponsor in connection with the development of the product. To allow for the use of information derived from the study, it is understood that the Investigator is obliged to provide the Sponsor with complete test results, all study data, and access to all study records.

Any results of medical investigations with the Sponsor's products and/or publication/lecture/manuscripts based thereon, shall be exchanged and discussed by the Investigator and Sponsor representative(s) 30 days before submission for publication or presentation. Due regard shall be given to the Sponsor's legitimate interests (eg, manuscript authorship, obtaining optimal patent protection, coordinating and maintaining the proprietary nature of submissions to health authorities, coordinating with other ongoing studies in the same field, and protecting confidential data and information.) The Sponsor shall be furnished with a copy of any proposed publication. Comments shall be rendered without undue delay.

In cases of publications or presentations of material arising from multicenter clinical investigations, the Sponsor is to serve as coordinator and referee. Individual Investigators who are part of a multicenter investigation may not publish or present data that are considered common to a multicenter investigation without the consent of the other participating Investigators and the prior review of the Sponsor.

In case of disagreement among the Investigators participating in a multicenter investigation, the Sponsor will be the final arbiter. Comments shall be given without undue delay. If they are not accepted, the senior author of the manuscript and representatives of the Sponsor shall promptly meet to discuss further and endeavor to agree mutually on the final wording and/or disposition of the publication. The above procedure also applies to information on prematurely discontinued and other non-completed studies.

Results from investigations shall not be made available to any third party by the investigating team outside the publication procedure as outlined previously. The Sponsor will not quote from publications by Investigators in its scientific information and/or promotional material without full acknowledgment of the source (ie, author and reference).

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ABBREVIATIONS

18F-FDG PET	18-fluorodeoxyglucose-positron emission tomography
λ_z	Terminal elimination rate constant
ACE	Angiotensin converting enzyme
ADA	Anti-drug antibodies
AE	Adverse Event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
$AUC_{0\text{-}t,norm}$	Dose-normalized $AUC_{0\text{-}t}$
$AUC_{0\text{-}\infty}$	Area under the serum XTMAB-16 concentration-time curve from time 0 (predose) to the last quantifiable concentration time point t, and extrapolated to infinity
$AUC_{0\text{-}\infty,norm}$	Dose-normalized $AUC_{0\text{-}\infty}$
$AUEC_{0\text{-}t}$	Area under the effect-time curve from time 0 (predose) to the last quantifiable effect-concentration time point, t
BMI	Body mass index
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practice
CL	Total body clearance after IV dosing
C_{max}	Maximum observed concentration

$C_{max,norm}$	Dose-normalized C_{max}
CMP	Clinical monitoring plan
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COP	Clinical operations plan
CRF	Case Report Form
CRO	Contract Research Organization
CRU	Clinical research unit
C_T	Serum concentration at the end of drug infusion
CV	Coefficient of variation
eCRF	Electronic Case Report Forms
ECG	Electrocardiogram
$E_{max,obs}$	Maximum observed effect
EOS	End of study
ES	Enrolled set
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FIH	First-in-human
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation

GLP	Good Laboratory Practices
gMean	Geometric mean
GMP	Good Manufacturing Practices
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HRT	Hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IFN-γ	Interferon gamma
IgG1κ	Immunoglobulin G 1 kappa
IL-6	Interleukin 6
IND	Investigational New Drug Application
IRB	Institutional Review Board
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean residence time
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
NOAEL	No adverse effect level
OHRP	Office for Human Research Protections

PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetics
PT	Preferred term
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
sIL-2R	Soluble IL-2 receptor
SoA	Schedule of Assessments
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reaction
sTNFα	Soluble tumor necrosis factor alpha
$t_{1/2}$	Terminal elimination half-life
TEAE	Treatment-emergent adverse event
$t_{Emax,obs}$	Time to reach maximum observed effect
TgTC	hTNFα transgenic mice
TK	Toxicokinetic
t_{max}	Time to reach maximum observed concentration
tmTNF	Transmembrane tumor necrosis factor
TNFα	Tumor necrosis factor alpha

TNF-R	Tumor necrosis factor receptor
ULN	Upper limit of normal
UP	Unanticipated Problem
US	United States
USP	United States Pharmacopeia
V_z	Volume of distribution during the terminal phase following IV dosing
WASOG	World Association of Sarcoidosis and other Granulomatous Disorders
WFI	Water for injection
WOCBP	Women of childbearing potential

11 REFERENCES

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APPENDIX 1: CLINICAL LABORATORY TESTS

The tests detailed in Table 7 will be performed by the central laboratory. The time points are specified in the SoA (Section 1.3).

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.

Additional tests may be performed at any time during the study as deemed necessary by the Investigator or required by local regulations.

Table 7 Clinical Laboratory Parameters

Hematology	Clinical Chemistry	Virology/Bacteriology	Urinalysis	Drugs of Abuse
Hematocrit Hemoglobin Platelet count Red blood cell count White blood cell count with differential: Neutrophils Eosinophils Basophils Monocytes Lymphocytes Activated partial thromboplastin time	Albumin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Bilirubin (total and conjugated) C-reactive protein Calcium Chloride Creatinine Creatine phosphokinase Gamma-glutamyl transferase Glucose Potassium Sodium Total cholesterol Total protein Triglycerides Tryptase[a] WOCBP Only (per SoA): Human chorionic gonadotropin	Hepatitis B surface antigen Hepatitis B core antigen antibody Hepatitis C virus antibody HIV antibody (HIV1 and HIV2) COVID-19 Tuberculosis (quantiFERON Gold™ test)	Protein Glucose Red blood cells White blood cells Ketone bodies pH At discretion of Investigator based on urinalysis results: Microbiology Urine microscopy	Alcohol Amphetamines/methamphetamines Barbiturates Benzodiazepines Cannabinoids Cocaine Opiates

a Tryptase will be assessed only at Baseline (for all participants) and in the event a participant experiences anaphylaxis (sample to be collected as soon as is reasonable after treatment.

APPENDIX 2: PHARMACOKINETIC, ANTI-DRUG ANTIBODY, AND BIOMARKER CYTOKINE COLLECTION TIME POINTS

Table 8 Pharmacokinetic, Anti-drug Antibody, Biomarker, and Telemetry Collection Time Points

a All sampling time points refer to time from the start of infusion.
b Inflammatory biomarkers analyzed include ACE, sIL-2R, IL-6, and sTNFα.
c Sampling window is -30 minutes.
d Sampling window is +5 minutes.
e Sampling window is ±5 minutes.
f Sampling window is ±15 minutes.
g Sampling window is ±30 minutes.
h Sampling window is ±1 hour.
i Sampling window is ±3 hours.
j At Weeks 3, 4, 6, 8, and 10, all efforts should be made to collect the PK and biomarker samples as close as possible to the target hour for sample collection. If needed, the samples can be collected up to 24 hours before or after the target sample time for the visit. Thus, the windows for sample collection are 314 to 362 hrs at Week 3, 650 to 698 hrs at Week 4, 986 to 1034 hrs at Week 6, 1322 to 1340 hrs at Week 8, and 1658 to 1706 hrs at Week 10. The exact time of sample collection must be recorded on the eCRF.

k Time-matched periods for telemetry data extraction corresponding to the projected time points on Day 1. The predose telemetry data extraction period on Day 1 should match the projected 24-hour time point after infusion.

APPENDIX 3: CONTRACEPTION

Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 90 days after the last dose of study drug, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either:

- Be abstinent from heterosexual intercourse with a woman of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.
- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below).

Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate whether she is of childbearing potential or is postmenopausal (see definitions below). A female participant of childbearing potential who is sexually active with a nonsterilized male partner **must** agree to use highly effective contraception from the time of signing the informed consent, throughout the duration of the study, and for 90 days after the last dose of study drug.

The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

a. Documented hysterectomy

b. Documented bilateral salpingectomy

c. Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Müllerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the CRU personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female.

    a. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:

        i. A high follicle stimulating hormone (FSH) level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or hormone replacement therapy (HRT).

        ii. Woman on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

Highly effective methods (according to Therapeutics Research Program Guidance for the Development of Protocol Procedures to Address Reproductive Risk, 21 Dec 2017):

- Bilateral tubal ligation or tubal occlusion
- An approved hormonal contraceptive such as oral contraceptives, patches, implants, injections, rings, or hormonally-impregnated intrauterine device (IUD)
- IUD
- Vasectomized partner
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm

has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

- Sexual abstinence
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

APPENDIX 4: TOXICITY GRADING FOR INJECTION SITE REACTIONS, VITAL SIGNS, AND LABORATORY PARAMETERS

Table 9 Grading for Injection Site Reactions

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Table 10 Grading for Vital Signs

Vital Signs *	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) ** (°F) **	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Subject should be at rest for all vital sign measurements.
** Oral temperature; no recent hot or cold beverages or smoking.
*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Table 11 Grading for Clinical Abnormalities

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

***ULN" is the upper limit of the normal range.

Source: FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers enrolled in Preventive Vaccine Clinical Trials. September 2007.

APPENDIX 5: CRITERIA FOR DIAGNOSING AND RECOMMENDED TREATMENT FOR ANAPHYLAXIS

Table 12 Clinical Criteria for Diagnosing Anaphylaxis

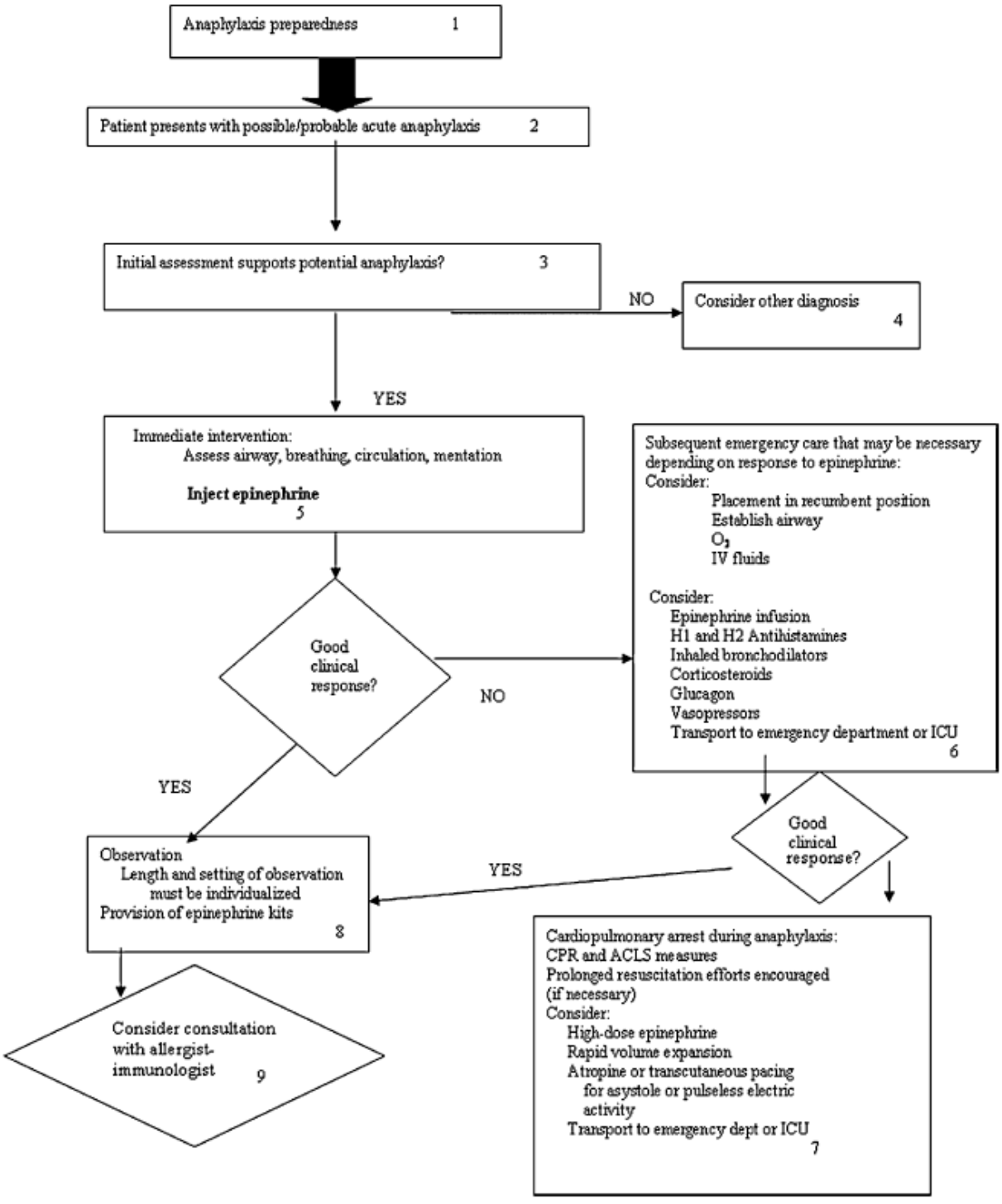
Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; *BP*, blood pressure.
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Source: Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: Summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *Am Acad Allergy, Asthma, Immunol*. 2006.

Figure 2 Algorithm for the Treatment of Acute Anaphylaxis



Abbreviations: ACLS = advanced cardiac life support; CPR = cardiopulmonary resuscitation; ICU = intensive care unit.

Source: Lieberman P, Kemp SF, Oppenheimer J, et al. The diagnosis and management of anaphylaxis: An updated practice parameter. *Am Acad Allergy, Asthma, Immunol*. 2005.