Parexel International

Xentria Inc.

XTMAB-16-101

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

Statistical Analysis Plan

Version: Final 3.0

Parexel Project Number: 251877

SPONSOR SIGNATURE PAGE

Approved by: _____ _____

[redacted] Date

Clinical Lead, Xentria, Inc.

Parexel SIGNATURE PAGE

Signatures below confirm that the Statistical Analysis Plan was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

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REVISION HISTORY

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Version No.	Effective Date	Summary of Change(s)
Final 1.0	Date of Last Signature	New Document
2.0	Date of Last Signature	Clarification added on Exposure Response QT analysis
3.0	Date of Last Signature	Addressed comments on Final 2.0

LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
ADA	Anti-drug antibody
AE	Adverse event
ATC	Anatomical therapeutic chemical
AUC	Area under the concentration-time curve
$AUC_{0\text{-inf}}$	Area under the serum concentration versus time curve extrapolated to infinity
$AUC_{0\text{-last}}$	Area under the serum concentration versus time curve from time zero to the last quantifiable time point at t
$\%AUC_{ex}$	Percentage of $AUC_{0\text{-inf}}$ that is due to extrapolation beyond Tlast
AUEC	Area under the effect time curve
BLQ	Below the lower limit of quantification
BMI	Body Mass Index
Bpm	Beats per minute
CI	Confidence interval
C_T	Serum concentration observed at the end of drug infusion, where T is the duration of infusion time
CL	Total body clearance of a drug from the serum
CRF	Case Report Form
C_{max}	Maximum observed concentration
CV	Coefficient of variation
DBP	Diastolic blood pressure
DNC_{max}	Dose normalized C_{max}
$DNAUC_{0\text{-last}}$	Dose normalized $AUC_{0\text{-last}}$
$DNAUC_{0\text{-inf}}$	Dose normalized $AUC_{0\text{-inf}}$
DRM	Data Review Meeting
ECG	Electrocardiogram
EOS	End-of-study
ET	Early termination
$E_{max,\ obs}$	Maximum observed effect
HBsAg	Hepatitis B surface antigen

Abbreviation / Acronym	Definition / Expansion
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed consent form
IMP	Investigational Medicinal Product
IV	Intravenous
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean residence time of the drug in the body
NA	Not available
nAb	Neutralizing antibody
NCS	Not clinically significant
NK	Not known
PD	Pharmacodynamic
PDS	Protocol Deviation Specification
PK	Pharmacokinetic
PKS	Pharmacokinetic analysis set
QT	The QT interval is measured from the beginning of the QRS complex to the end of the T wave
QTc	corrected QT interval
QTcB	QT corrected using Bazzett's formula
QTcF	QT corrected using Fridericia's formula
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System Organ Class
$t_{½}$	Terminal half-life associated with the terminal phase
TEAE	Treatment-emergent adverse event
$t_{Emax,obs}$	Time to reach maximum observed effect

Abbreviation / Acronym	Definition / Expansion
t_{max}	Time to maximum observed concentration
V_z	Volume of distribution during the terminal phase
V_{ss}	Steady state volume of distribution following IV dosing
WHO-DD	World Health Organisation - Drug Dictionary
λ_z	Terminal elimination rate constant

1 INTRODUCTION

XTMAB-16 is a chimeric human-murine IgG1κ anti-TNFα monoclonal antibody. The final dosage form is a sterile, white, lyophilized powder for intravenous (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.

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. Participants will receive a single IV infusion of 2 or 4 mg/kg of XTMAB-16 or placebo on Day 1.

The Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing study data related to safety, pharmacokinetic (PK) and outlines the statistical programming specifications for the Tables, Listings and Figures (TLFs).

The analyses described in this SAP are based upon the following study documents:

- Study Protocol, Version 4.0, Amendment 3 (May 28, 2021)

This SAP will be finalized prior to database lock. Any changes after the finalization of this SAP will be documented in Statistical Method Modification Form.

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

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.

2.2 Secondary Objective(s)

Not Applicable.

2.3 Exploratory Objective(s)

Not Applicable.

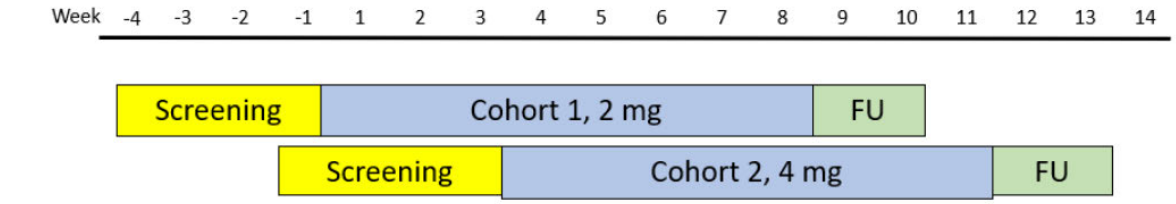
3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

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 1. Participants will receive a single IV infusion of 2 or 4 mg/kg of XTMAB-16 or placebo on Day 1.

Figure 3-1 Study Design



Abbreviations: FU = follow-up.

Table 1 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.

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, 4:1 for remaining participants) and administered study drug on Day 1. Participants will remain at the CRU through Day 8 for PK, biomarkers, anti-drug antibody (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, 12-lead electrocardiogram (ECG), and physical examination. Samples for PK, Pharmacodynamic (PD) and immunogenicity will be collected and analysis will also be completed during the course of this study.

3.1.1 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 (e.g., 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 next Section.

3.1.2 Unblinding Procedure

Treatment assignment will be double-blind. Investigators, participants, CRO, and sponsor will be blinded throughout the study. Actual treatment assignment will be available after the occurrence of database lock for the purpose of performing statistical analyses of clinical trial data.

3.1.3 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 serious Adverse Events (AEs) , Serious Adverse Events (SAEs) and/or treatment-emergent AEs (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).

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 as per stopping rule mentioned in protocol.

3.2 Endpoints and Associated Variables

3.2.1 Primary 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 parameters by visit.
- Time-matched Baseline and 50-hr post dose digital ECG parameters monitoring.
- Observed values and change from Baseline in vital signs.

Immunogenicity

- Number and percentage of participants by cohort who test positive for XTMAB-16 anti-drug antibody (ADA) at Baseline, Day 29, Day 57, and Day 71
- Number and percentage of participants by cohort who test positive for XTMAB-16 neutralizing antibody (nAb) at Baseline, Day 29, Day 57, and Day 71

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 TNFα (sTNFα)

Other relevant biomarkers may be assessed to better understand PK/PD relationships.

3.2.2 Secondary Endpoints

Not Applicable

Pharmacokinetics

Serum PK of XTMAB-16 will be assessed after single dose administration of XTMAB-16 as below:

- C_{max}: Maximum observed XTMAB-16 serum concentration
- C_T: XTMAB-16 serum concentration at the end of drug infusion
- t_{max}: Time to maximum observed XTMAB-16 concentration
- $AUC_{0\text{-}inf}$: Area under the XTMAB-16 concentration-time curve from time zero extrapolated to infinity
- $AUC_{0\text{-}last}$: Area under the XTMAB-16 concentration-time curve from time zeroto the last quantifiable concentration
- CL: Systemic clearance after IV dosing
- λ_z: Terminal elimination rate constant
- $t_{1/2}$: Terminal elimination half-life calculated as: $\ln 2/\lambda_z$
- V_z: Volume of distribution during the terminal phase calculated as: $Dose/(\lambda_z \cdot AUC_{0\text{-}inf})$
- V_{ss}: Steady state volume of distribution following IV dosing calculated as: MRT·CL
- MRT: Mean residence time

*Dose normalized C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$ will be also calculated

3.2.3 Exploratory Endpoints

Not Applicable

3.2.4 Safety Variables

- Vital signs (supine blood pressure [BP] and pulse, tympanic (ear), oral and temporal body temperature, respiratory rate)
- 12-lead electrocardiograms (ECG): P wave, QRS complex, U wave, QRS duration, QT interval, QTcF, T wave, ST segment, RR interval, PR interval, and qualitative results.
- Telemetry
- Clinical laboratory tests (hematology, biochemistry, urinalysis, Virology, Urine Drug abuse Screening, Serum Pregnancy Test)
- Adverse event (AE) assessments
- Physical examinations

3.2.5 Pharmacodynamic Variables

Not Applicable

3.2.6 Immunogenicity Variables

Immunogenicity testing XTMAB-16 of ADA and nAb using designated serum samples from each participant is planned to be conducted.

An individual sample result will be designated “antibody positive” based on both positive screening and confirmation assay results (i.e., confirmed positive result), and otherwise will be deemed “antibody negative” or “inconclusive.” The titer assay will be performed for antibody-positive samples. For (anti-drug XTMAB-16 antibodies) positive samples, the presence of neutralizing antibodies may be determined using the (anti-drug XTMAB-16 antibodies) neutralizing assays.

Study participants will be given "positive" status if they have at least one antibody positive sample result at any time post baseline (during either the Treatment and Observation Period or the Safety Follow-up Period). A study participant will be given "negative" status if all evaluated immunogenicity sample results during the Postbaseline Period are antibody negative.

The antibody response in antibody-positive participants can be further classified by the following criteria:

- "Treatment-induced": Has at least one antibody positive sample at any time after treatment (for participants with antibody-negative status at Baseline)
- "Treatment-boosted": Has at least one antibody-positive sample at any time after treatment with a titer of four-fold or greater compared to Baseline (for participants with antibody-positive status at Baseline)

3.2.7 Pharmacokinetic Variables

Blood samples will be collected for XTMAB-16 PK analysis at pre dose (Hour 0), at 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 hours (Week 4, Day 29), 1010 hours (Week 6, Day 43), 1346 hours (Week 8, Day 57), and 1682 hours (Week 10, Day 71) post infusion 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 Window Allowance Document. The exact time of sample collection must be recorded on the eCRF.
Unless otherwise stated, derivation of PK parameters will be the responsibility of Clinical Pharmacology, Modeling and Simulation (CPMS, formerly Quantitative Clinical Development (QCD), Parexel International. If calculable, the PK parameters listed in (Table 2) will be determined for XTMAB-16 in serum following single IV dose administration:

Table 2 Pharmacokinetic Parameters after Single Dose Administration

Parameter	Definition
C_T	XTMAB-16 serum concentration at the end of drug infusion
C_{max}	Maximum observed serum concentration determined directly from the concentration-time profile
t_{max}	Time of maximum serum concentration determined directly from the concentration-time profile
$AUC_{0\text{-}inf}$	Area under the concentration-time curve from time zero extrapolated to infinity
$AUC_{0\text{-}last}$	Area under the concentration-time curve up to last measurable concentration
λ_z	Terminal elimination rate constant
$t_{½}$	Terminal elimination half-life calculated as: $\ln 2/\lambda_z$

Parameter	Definition
CL	Total body clearance calculated as: Dose/AUC_{inf}
V_z	Volume of distribution during the terminal phase calculated as: Dose/($\lambda_z \cdot AUC_{0\text{-}inf}$)
MRT	Mean residence time of the drug in the body
V_{ss}	Steady state volume of distribution following IV dosing calculated as: MRT·CL
DNC_{max}, $DNAUC_{0\text{-}last}$, $DNAUC_{0\text{-}inf}$	Dose-normalized C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$

Additional PK parameters may be calculated if needed.

3.2.8 Biomarker Variables

Absolute and percent change from baseline in the following biomarkers will be analyzed.

- Angiotensin converting enzyme (ACE)
- soluble IL-2 receptor (sIL-2R)
- Interleukin 6 (IL-6)
- soluble TNFα (sTNFα)

Biomarker samples will be corrected for biomarker analysis at pre dose (Hour 0), and at 8 hours on Day 1, 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 hours (Week 4, Day 29), 1010 hours (Week 6, Day 43), 1346 hours (Week 8, Day 57), and 1682 hours (Week 10, Day 71) post infusion of XTMAB-16 or placebo. All sampling time points after time T refer to time from the start of infusion.

Unless otherwise stated, derivation of biomarker parameters will be the responsibility of Clinical Pharmacology, Modeling and Simulation (CPMS, formerly Quantitative Clinical Development (QCD), Parexel International. The following biomarker parameters, if data permit, will be determined for XTMAB-16 in serum following single IV dose administration:

Table 3 Biomarker Parameters after Single Dose Administration

Parameter	Definition
AUEC	Area under the effect-time curve
$E_{max,obs}$	Maximum observed effect
$t_{Emax,obs}$	Time to reach maximum observed effect

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard Parexel procedures.

4.2 General Presentation Considerations

This section is applicable to all non-PK assessments.

TLF outputs will be generated for XTMAB-16 and pooled placebo by the planned treatment duration.

The participants, who received "Placebo" in each cohort, will be pooled into a single placebo group (Pooled Placebo) in each respective part for all summaries and presentation related to safety for this study. The PK outputs will be generated for each XTMAB-16 dose.

'Baseline' is defined as the last observed value of the parameter of interest prior to dosing (this includes unscheduled visits) for each XTMAB-16 dose and pooled placebo group. 'End of Study' for a participant is defined as the last available post-treatment assessment. 'Study Day' will be calculated relative to the date of randomization i.e. Study Day = Assessment Date -Randomization Date + 1.

In case of any unscheduled repeated assessments occurred during the period, the following rule will be applied, unless specified otherwise:

If unscheduled repeated measurement of a specific parameter occurs prior to the first XTMAB-16 administration (Day 1), then the last obtained value prior to dosing will be considered in the descriptive statistics and in the calculation of change from baseline.

If unscheduled repeated measurement of a specific parameter occurs after Day 1 or XTMAB-16 or Placebo administration, then the first (non-missing) value after dosing will be used in descriptive statistics and in the calculation of change from baseline.

All data will be listed according to the number of decimal places presented in the source data with a limitation on maximum of 3 decimal places. Continuous data will be summarized in terms of the mean, standard deviation (SD), median, minimum, maximum and number of observations, unless otherwise stated.

The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean and median will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Departure from these general rules will be specified in the output shell document.

Categorical data will be summarized in terms of the number of participants providing data at the relevant time point (n), frequency counts and percentages. Any planned collapsing of categories will be detailed in the SAP text and the data displays.

Percentages will be presented to one decimal place. Percentages as "0.0" will be presented for zero counts. Percentages will be calculated using n as the denominator. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only.

Changes from baseline in categorical data will be summarized using shift tables where appropriate. Confidence intervals will be presented to same decimal place as of associated estimate.

4.3 Software

All report outputs will be produced using SAS® version 9.4 or a later version in a secure and validated environment.

PK analyses will be produced using Phoenix® WinNonLin version 8.2 or a later version in a secure and validated environment.

All report outputs will be provided to the Sponsor in Microsoft Word document/RTF format.

4.4 Study Participants

4.4.1 Disposition of Participants

A clear accounting of the disposition of all participants who entered into the study will be provided, from screening to study completion.

The participant disposition summaries may include the following:

- A summary of the number of participants screened for entry into the study and the number and percentage of screened failure participants, number and percentage of participants randomized and dosed will be presented for all screened population by XTMAB-16 dose/ pooled placebo group and overall.
- All screened failure participants who did not meet the inclusion criteria and participants who did meet the exclusion criteria will be listed.
- The number and percentage of participants who completed the trial and those who discontinued study (including reasons for early withdrawal) will be presented by XTMAB-16 dose / pooled placebo group for all randomized set.
- Participant disposition will be listed for each participant, including the participant completion status, reason of discontinuation, date of discontinuation on all randomized population set.
- A randomization listing will be presented and include the following: each participant's randomization number, the participant's full Screening number, the treatment to which the participant has been randomized and the location of the clinical unit.

Primary reason of study discontinuation, as recorded on eCRF will be presented as one of the following:

- Adverse Event
- Death
- Loss to Follow-up
- Protocol Violation
- Participant withdrew at own request
- Other

4.4.2 Protocol Deviations

Protocol deviations defined as those deviations from the clinical study protocol relating to a participant likely to have an impact on the perceived pharmacokinetic, pharmacodynamic and safety of study treatments and include the following:

- Inclusion/exclusion criteria deviations
- Dosing deviations (e.g., incorrect treatment received, participant was not fasted as per the protocol requirements prior to and after dosing).
- Time window deviations for safety.
- Participants receiving prohibited concomitant medications.
- Sample processing
- Other procedural and study conduct deviations recorded by the Clinical Unit on a protocol deviation log.

Protocol deviations that may potentially impact PK parameter derivations include, but are not limited to:

- More than three emetic episodes and the volunteer was not discontinued
- Missed PK samples that are evaluated to impact estimation of PK parameter(s)
- Time window deviation for PK samplings that may impact the estimation of PK parameter(s).
- Concomitant medications not authorized by protocol (drugs of abuse)

The criteria for the assessment and reporting of protocol deviations will be stipulated in a separate study specific protocol deviation specification (PDS) document. This will include a Windows Allowance Document (WAD) which stipulates tolerance windows for safety and PK assessments. Measurements performed within these tolerance windows will not be considered as protocol deviations and will not be reported as such.
All protocol deviations will be discussed at the data review meeting prior to final database hard lock in order to define the analysis population for the study. Prior to database lock, protocol deviation and analysis population outputs will be produced and will be sent to Sponsor for review. Analysis population classifications will be discussed in Data Review Meeting to discuss the outputs and to decide which participants and/or participant data will be excluded from certain analyses.
Protocol Deviation will be classified as Major/Minor. Minor deviations are defined as those that deviate from accepted procedures that will not adversely affect subject/data, but should be dealt with appropriately. Major deviations are defined as those that deviate from the protocol that are likely to have an impact on the participants rights, safety, well-being, and/or on the validity of the data for analysis.
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. 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.

All protocol deviations will be listed by participant on all full analysis sets. Protocol Deviations related to COVID-19 will be listed separately.

4.5 Analysis Sets

Following analysis, sets are defined in this study.

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. If all participants in the FAS received actual study drug as randomly assigned, summaries of demographics and baseline characteristics will not be presented for the Safety Set.

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 post dose without important protocol deviations related to study drug administration that would affect the concentration.

Participants who receive placebo will not be part of the statistical analysis and summary statistics for PK data. PK-PPS will be used to conduct the PK analysis to calculate PK parameters, descriptive summaries of PK parameters, statistical analysis for comparison of PK parameters, and create Tables and Figures. PK-PPS will be finalized after unblinding of the study. Any data excluded will be discussed in the CSR. Any excluded subject must have their concentration and PK parameter data listed only and footnoted with reason of exclusion.

Biomarker Set: All participants 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.

A summary of classification to analysis population will be presented in a listing by participant including reason of exclusion on all randomized population set. The number and percentage of participants included in each analysis population will be summarized on all randomized population set by dose cohort/ pooled placebo group and overall.

4.6 Demographics and Baseline Characteristics

Demographic and anthropometric variables (age, sex, ethnicity, race, height, weight and BMI) will be listed by participant. Demographic characteristics (age, sex, ethnicity and race) and anthropometric characteristics (height, weight and BMI) will be summarized by XTMAB-16 dose / pooled placebo group and overall, for all participants in the safety analysis set. The denominator for percentages will be the number of participants in the safety analysis set for each treatment or for all participants as applicable.

Age will be calculated as the number of complete years between a participant's birth date and the date of informed consent.

4.7 Medical History and Concomitant Illnesses

Medical history data will be listed by participant including visit, description of the disease/procedure, Medical Dictionary for Regulatory Activities (MedDRA Version 24.0 or latest) system organ class (SOC), MedDRA preferred term, start date, and stop date (or ongoing if applicable).

4.8 Prior and Concomitant Medications

Prior medications are those that started and stopped prior to the dose of IMP. Concomitant

medications are those taken before or after dosing (including medications that started prior to dosing and continued after) and up to end of trial.

Prior and concomitant medications will be presented based on safety analysis population and will be listed by participant and will include the following information: reported name, preferred term, the route of administration, dose, frequency, start date/time, duration, and indication.

Prior and concomitant medication will be coded according to the World Health Organization Drug Dictionary (WHO-DD) (Version March 1, 2021 B3 or latest) and will be classified by Anatomical Therapeutic Chemical (ATC) categories.

If missing data prevents the medication being classified as prior or concomitant, the medication will be considered as concomitant for the data listings.

Medication start and stop dates will be compared to the date of dose of study medication to allow medications to be classified as either Prior only, or Concomitant only. Medications starting after the completion/withdrawal date will be listed but will not be classified or summarized.

Medications that start and stop prior to the date of dose of study medication will be classified as Prior only. Medications will be classified as Concomitant only if they have a start date before or after the date of dose of study medication and up to end of trial.

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of dose of study medication. Medications will be assumed to be Concomitant only, unless there is clear evidence (through comparison of partial dates) to suggest that the medication started prior to the dose of study medication. If there is clear evidence to suggest that the medication stopped prior to the dose of study medication, the medication will be assumed to be Prior only.

4.9 Treatment Exposure

A listing of drug administration will be created and will include the dose cohort, treatment received, date and time of administration, dose (unit), dose form, route of administration.

4.10 Pharmacokinetic Evaluation

4.10.1 Pharmacokinetic Concentrations

Concentration Listings:

Pharmacokinetic concentration data for XTMAB-16, will be listed by treatment and subject for the Safety Set. Concentration listings will include nominal PK sampling time, actual sampling time relative to start of infusion, infusion duration, deviation from start of nominal infusion time, percent deviation from nominal time and concentrations. Serum concentrations below the lower limit of quantification (LLOQ) will be presented as below the limit of quantification (BLQ) in the listings and the LLOQ value presented as a footnote. Missing PK samples will be reported as no sample (NS) and/or not reportable (NR) and considered excluded from PK analysis.

Concentration Summary tables:

Source data as reported from the laboratory will be used for calculation of concentration summary statistics. Tabular summaries for concentration-time data will report N (number of participants who received treatment), n (number of participants with non-missing values)), and n(BLQ) (the number of participants with BLQ).

Serum concentrations for XTMAB-16 will be summarized by treatment, and nominal timepoint using the PK-PPS set. The following descriptive statistics will be presented for serum concentrations obtained at each nominal time point: N, n, n(BLQ), arithmetic mean, SD, coefficient of variation (CV%), geometric mean, geometric CV% (calculated as: gCV% =SQRT(es^2 -1)*100; where s is the standard deviation of the log-transformed values), median, minimum and maximum values.

For summary tables, all BLQs will be considered zero, and the number of BLQs and non-BLQs at each scheduled time point will be reported. Summary Statistics will not be calculated if non-BLQ concentrations at a scheduled time point is <3 and will be reported as NC. If for any time point any value is zero in this case Geometric mean and Geometric CV(%) for respective time point will not be calculated and reported ad NC.

The rules followed for calculation and presentation of concentration data with regards to the number of decimal places/significant digits for the listings of subject level concentrations and summary tables of concentration are as follows:

Table 4 Rounding Rules for Concentration Listings and Tables

Serum Concentration Listings and Tables	Rounding
Individual concentrations	*n* s f. as supplied by bioanalytical laboratory
Minimum and Maximum	*n* s.f. capped at 4
Mean/SD/Median/Geomean	*n+1* s.f. capped at 4
CV%/gCV%	*1* d.p.
N/n	Whole number

s f = significant figures, d.p. = decimal place

Concentration Figures:

For arithmetic mean linear/linear graphs, all BLQ values will be substituted with zero for calculation of arithmetic mean and for log/linear graphs the log transformed arithmetic mean will be displayed (this should not include zero).

Individual linear/linear and log/linear graphs all BLQ values will be substituted as follows:

- BLQs at the beginning of a subject profile (ie, before the first incidence of a measurable concentration) will be assigned to zero (except for intravenous administration when these BLQs should not be displayed). When using log/linear scale, these timepoints will be considered missing.
- BLQs at the end of a subject profile (ie, after the last incidence of a measurable concentration) will be set to missing.
- Single BLQs which fall between two measurable concentrations will be set to missing.
- Consecutive BLQs which fall between measurable concentrations will be set to missing. Measurable concentrations after consecutive BLQs will be set to missing.

To visualize subject-level concentrations and the comparison between each cohort, the descriptive PK graphs listed below will be generated.

- Figure xx.1: Individual XTMAB-16 Serum Concentration-Time Profiles (Linear and Semi-Logarithmic Scale), (Safety Set)
- Figure xx.2: Combined Individual XTMAB-16 Serum Concentration-Time Profiles (Linear and Semi-Logarithmic Scale) by Treatment, (Safety Set)
- Figure xx.3: Mean (± SD) XTMAB-16 Serum Concentration-Time Profiles (Linear and Semi-Logarithmic Scale) by Treatment, (PK-PPS)

Figures will be generated in black and white or color using unique line style and marker for each plot in the graph. Actual times will be used for individual and combined individual serum concentration-time profiles on Safety Set, and nominal times will be used for mean (± SD) serum concentration-time profiles (no SD for semi-logarithm plot) on PK-PPS. All plots will be presented on a linear and semi-logarithm scale.

4.10.2 Pharmacokinetics Parameters

Pharmacokinetic parameters will be calculated by non-compartmental analysis methods from the concentration-time data using Phoenix® WinNonlin® (Version 8.2) or higher following these guidelines:

- Actual sampling times relative to the start of infusion rather than nominal times will be used in the calculation of all derived pharmacokinetic parameters except when parameters are calculated for safety/dose escalation meetings when nominal times may be used to calculate PK parameters.
- There will be no imputation of missing data.
- Handling of BLQ data for the derivation of serum PK Parameters
  - BLQs at the beginning of a subject profile (i.e. before the first incidence of a measurable concentration) will be assigned to zero.
  - BLQs at the end of a subject profile (i.e. after the last incidence of a measurable concentration) will be set to missing.
  - Single BLQs which fall between two measurable concentrations will be set to missing.
  - Consecutive BLQs which fall between measurable concentrations will be set to missing. Measurable concentrations after consecutive BLQs will also be set to missing.

Pharmacokinetic parameters will be estimated according to the guidelines presented in Table 3.

Table 5 Pharmacokinetic Parameter and Estimation

Parameter	Guideline for Derivation
C_{max}, t_{max}, C_T	Obtained directly from the observed concentration-time data.
AUC_{0-t} or AUC_{0-last}	The AUC from zero time (pre-dose) to the time of last quantifiable concentration will be calculated by a combination of linear and logarithmic trapezoidal methods. Unless specifically requested and justified, the linear up/log down trapezoidal method will be employed. The AUC_{0-t} is the sum of areas up to the time of the last quantifiable sample: $AUC_{0-t}=\int_0^t C_{last} * dt$

Parameter	Guideline for Derivation
$AUC_{0\text{-inf}}$	The area from zero time extrapolated to infinite time will be calculated as follows: $AUC_{0\text{-}inf} = AUC_{0\text{-}t} + \frac{C_{last}}{\lambda_z}$ where C_{last} is the last observed quantifiable concentration.
$\%AUC_{ex}$	The percentage of $AUC_{0\text{-inf}}$ obtained by extrapolation will be calculated as follows: $\%AUC_{ex} = \frac{AUC_{0\text{-}inf} - AUC_{0\text{-}t}}{AUC_{0\text{-}inf}}$ x100 . Unless otherwise determined by PK Scientist's best knowledge and judgment, if the $\%AUC_{ex}$ is greater than 30% the value, $\%AUC_{ex}$, and all dependent parameters (ie, $AUC_{0\text{-inf}}$, MRT, Vz and CL) will be flagged in listings and excluded from summary tables and statistical analysis of PK parameters. The reason for exclusion will be listed/footnoted in parameter listings.
λz and t½	1. The apparent terminal phase rate-constant (λz) will be estimated by linear regression of concentration versus time data presented in a log-linear scale. 2. Data are primarily monotonically decreasing in magnitude and are representative of the actual decline in the log concentration-time curve. 3. Only those data points that are judged to describe the terminal log-linear decline will be used in the regression. 4. A minimum number of three data points in the terminal phase will be used in calculating λz with the line of regression starting at any post-C_{max} data point (C_{max} should not be part of the regression slope, if possible). Unless otherwise determined by PK Scientist's best knowledge and judgment, if the adjusted correlation coefficient (R^2 adjusted) is <0.8, it will be excluded from the summary tables and statistical analysis of PK parameters, and λz and all the λz dependent parameters (i.e. t½, $AUC_{0\text{-inf}}$, CL, MRT, and Vz) will also be flagged and excluded from summary tables and statistical analysis. The reason for exclusion will be listed/footnoted in parameter listings. 5. Unless otherwise determined by PK Scientist's best knowledge and judgment, the interval used to determine λz should be equal or greater than 1.5-fold the estimated t½, and if less than 1.5-fold, λz will be flagged in listings and excluded from summary tables and statistical analysis of PK parameters. All the derived parameters (i.e. t½, $AUC_{0\text{-inf}}$, CL, MRT, and Vz) will also be flagged from listings and excluded from statistical analysis of PK parameters. The reason for exclusion will be listed/footnoted in parameter listings. 6. The t½ will be calculated as follows: $t½ = \ln 2/\lambda z = 0.693/\lambda z$ 7. Data points may be dropped from the linear regression if the PK Scientist considers the reported values to be anomalous. Any data points so designated should remain in the listings with a footnote and be identified in the study report with a rationale for exclusion.
CL	Following IV administration, systemic clearance of drug will be calculated from: $CL = \frac{Dose}{AUC_{0\text{-}inf}}$
V_z	Volume of distribution at terminal phase following IV dosing may be calculated from: $V_z = \frac{Dose}{\lambda_z \times AUC_{0\text{-}inf}} = CL / \lambda_z$
V_{ss}	Following IV administration, the volume of distribution at steady state of drug will be calculated from: $V_{,ss} = CL \times MRT_{iv}$
MRT	Mean residence time of the drug is calculated as: $MRT = [AUMC_{0\text{-}inf}/AUC_{0\text{-}inf} - TI/2]$ where $AUMC_{0\text{-inf}}$ is area under the serum concentration moment (C · t) versus time curve extrapolated to infinity according to the following equation: $AUMC_{0\text{-inf}} = AUMC_{0\text{-}t} + (Ct \cdot t / \lambda z + Ct / \lambda z^2)$ TI is the length of infusion
DNC_{max}, $DNAUC_{0\text{-last}}$, $DNAUC_{0\text{-inf}}$	Dose-normalized C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-inf}}$ calculated as: parameter value/Dose

PK Parameters Listings:
Pharmacokinetic parameters will be listed by treatment and subject for the Safety Set. PK parameters that will be excluded from summary tables and statistical analyses of PK parameters will be flagged and footnoted with reason for exclusion.
PK Parameter Summary Tables:
PK parameters will be provided by CPMS group. Biostatistics group will consider this the PK parameters source data and will use this data without rounding for calculation of PK parameter summary statistics tables.
PK parameters will be summarized by treatment for the PK-PPS.
Tabular summaries for PK parameters will report N (number of participants who received treatment) and n (number of participants with non-missing values).
Descriptive statistics for calculated PK parameters will include: N, n, arithmetic mean, SD, CV%, geometric mean, geometric CV%, median, minimum and maximum values. For t_{max}, only median, minimum and maximum values will be presented. No descriptive statistics will be determined when fewer than three individual PK parameters are available.
The rules followed for presentation of PK parameters data with regards to the number of decimal places/significant digits for the listings of subject level PK parameters and summary tables of PK parameters are as follows:

Table 6 Rounding Rules for PK Parameter Listings and Tables

PK Parameter Listings and Tables	Rounding
Derived Individual parameters	4 s f.
Directly Derived Individual parameters (C_{max}, C_T)	*n* s f. as supplied by the analytical laboratory but not more than 4 s f.
Minimum and Maximum	4 s f.
Mean/SD/Median/Geomean	4 s f.
CV%/gCV%	1 d.p.
Comparative estimates	3 d.p.
CI and other percentages	2 d.p.
p-values	4 d.p.
N/n	Whole number
Exceptions for PK Tables	
t_{max} individuals and min/max	2 d.p
t_{max} median only	2 d.p

s f = significant figures, d.p. = decimal place

PK Parameter Figures:

The following plots will also be generated:

- Boxplots for dose normalized PK parameters (e.g., C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$) versus treatment

Assessment of Dose Proportionality

- Power Model using ANOVA Method:

An ANOVA of the natural log-transformed PK parameters, ln-transformed dose as a fixed and participant as random effect.

Dose-proportionality based on the power model will be accepted ("not rejected", in terms of statistical inference) if each of the 95% CIs of the slope of the effect of dose level on each of PK parameters includes 1.

For each of the parameters (C_{max} and AUCs) a plot of the log-transformed PK parameter against the log-transformed dose will be constructed including the fitted line from the linear regression and the line of unity.

Sample SAS Code:

```
ODS OUTPUT lsmeans=lsm estimates=est Diffs=diff1;

PROC MIXED DATA=PKDATA;

BY ANALYTE PKPARAM ;

CLASS SUBJECT;

MODEL LN_PK= LNDOSE/ddfM=KR;

RANDOM SUBJECT;

ESTIMATE "LNDOSE" LNDOSE/CL= 0.05;

RUN;
```

where:

LN_PK: natural log-transformed PK parameter

LNDOSE: natural log-transformed dose level of <drug>

ANALYTE: analyte (LICO FG-459)

PKPARAM: PK parameter

SUBJECT: participant

4.11 Safety Evaluation

All safety summaries and analyses will be based upon the Safety Set. All Safety and tolerability parameters (AEs, laboratory data (hematology, biochemistry, and urinalysis parameters), vital signs, physical exam findings and ECG parameters will be evaluated as following.

4.11.1 Adverse Events

An AE is any untoward medical occurrence in a study participant administered an IMP which does not necessarily have a causal relationship with this treatment.

A treatment-emergent adverse event (TEAE) is defined as an AE that begins or that worsens in severity after at least one dose of the study drug has been administered.

All related TEAEs will be defined as Adverse drug reaction (ADR).

Any AEs with incomplete start and end dates/times will be treated as follows:

- Adverse events with unknown start times, but with start date known, will be imputed with a time of 00:00, unless the start date corresponds to any given dosing date. In this case the start time will be imputed with the time of dosing. If this results in a start date/time after end date/time of the AE, then the time will also be imputed with 00:00.
- Adverse events with completely unknown start dates will be imputed with the date and time of first dosing, unless the end date is known and prior to dosing; in that case the start date will be imputed as the date of Screening and a time of 00:00.
- Adverse events with partially known start dates/times will be treated as follows:
  - If only the day is missing, then the day will be imputed with the first day of the month, unless the month and year in which the AE started is a month and year in which study drug was administered, then the day will be imputed with the first day on which study drug was administered in that month. If this results in a start date after the end date, then the day will be imputed with the first day of the month.
  - If only the month is missing, and the year is a year in which study drug was administered, then the month will be imputed with the first month in which study drug was administered. If this results in a start date after the end date of the AE, then the month will be imputed with JAN. If the known year part is not a year in which study drug was administered, then the month will also be imputed with JAN.
  - If both the day and month is missing and the year is a year in which study drug was administered, then the day and month will be imputed with the day and month of dosing. If this results in a start date after end date, then the day and month will be imputed with 01JAN. If the year is not a year in which study drug was administered, then the day and month will also be imputed with 01JAN.
  - If only the year is missing, then the year will be imputed with the year of dosing.

Unknown dates and times will be shown as NK and NK:NK in the listings (where NK = Not Known), respectively.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 or higher.

Unless specified otherwise, all adverse event summaries will include the TEAEs only and adverse event summary counts will be the number of participants reporting adverse events and not the number of events reported.

If more than one event occurred with the same preferred term for the same participant, then the participant will be counted only once for maximum severity level or for most causality level of that preferred term for the summarization of severity or causality accordingly. This table will be sorted alphabetically by SOC and PT.

The following summaries will be presented:

- A table of number (percentage) of participants and number of adverse events with an overview of treatment emergent adverse events (TEAE), severe AEs,ADR, SAE, and AE leading to discontinuation will be presented by XTMAB-16 dose, pooled placebo and overall.
- A table of number (percentage) of participants and number of adverse events with treatment emergent adverse events (TEAE), and SAE summarized by SOC and PT, XTMAB-16 dose, pooled placebo and overall. This table will be sorted by decreasing frequency of the overall column.
- A table of number (percentage) of participants and number of adverse events with TEAEs summarized by SOC, PT, relationship, XTMAB-16 dose, pooled placebo and overall. If more than one event with the same preferred term occurred for the same participant, then the participant was counted only once for that preferred term under the strongest causality. This table will be sorted by decreasing frequency of the overall column.
- Tables of number (percentage) of participants and number of adverse events with TEAEs summarized by SOC, PT maximum severity, XTMAB-16 dose, pooled placebo and overall will be presented. If more than one event occurred with the same preferred term for the same participant, then the participant was counted only once for maximum severity level of that preferred term for the summarization of severity. This table will be sorted by decreasing frequency of the overall column.
- A listing will be created for all Adverse Events (AEs), which will include: treatment received, treatment period, preferred term (PT), system organ class (SOC), AE onset date (and time), AE end date (and time), measure taken on AE, relationship to IMP, AE outcome, severity, frequency, action taken, concomitant medication (if administered), TEAE indicator flag and SAE indicator flag.
- A table of grading of injection site reaction (Table 5) will be summarized by dose cohort and overall.
- A by subject listing of TEAE leading to discontinuation, TEAE expectedness and SAE will be created.

Adverse event summaries will be ordered in terms of decreasing frequency for SOC, and PT within SOC, and then alphabetically for SOC, and PT within SOC.

4.11.2 Deaths, Serious Adverse Events, and Adverse Events of Special Interest

A by-participant listing of death, adverse of special interest (AESI) and all serious adverse events will be created.

4.11.3 Clinical Laboratory Evaluation

The following safety laboratory parameters will be measured:

Hematology: Hematocrit, Hemoglobin, Platelet count, Red blood cell count, White blood cell count with differential, Neutrophils, Eosinophils, Basophils, Monocytes, Lymphocytes, Activated partial, thromboplastin time.

Clinical Chemistry: 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, Tryptasea, WOCBP Only (per SoA): Human chorionic, gonadotropin.

Viral Serology: Hepatitis B surface antigen, Hepatitis B core antigen antibody, Hepatitis C virus antibody, HIV antibody (HIV1 and HIV2), COVID-19, Tuberculosis (quantiFERON Gold™ test).
Urinalysis: Protein, Glucose, Red blood cells, White blood cells, Ketone bodies, pH.
At discretion of Investigator based on urinalysis results:

- Microbiology
- Urine microscopy

Drugs of Abuse: Alcohol, Amphetamines/methamphetamines, Barbiturates, Benzodiazepines, Cannabinoids, Cocaine, Opiates.

Individual data listings of all the laboratory results will be presented for each participant. Flags will be attached to values outside of the laboratory's reference limits along with the investigator's assessment. Clinically significant laboratory test abnormalities that were considered adverse events by the investigator will be presented in the adverse event listings.

Any laboratory parameters with results from the laboratory given as '<xx' or '>xx' in the database will be imputed with the absolute value of the number without the sign (e.g., < 9.2 will be imputed as 9.2) for the descriptive statistics and changes from baseline.

Safety laboratory tests (observed values and change from baseline) will be summarized descriptively in tabular format by dose cohort and pooled placebo group. The baseline for the laboratory parameters will be the measurement obtained prior to administration of IV of XTMAB-16. .

In order to compare a before-and-after effect for selected laboratory parameters, shift tables with regards to reference ranges will be provided for each dose step, and for all participants.

The number and percentage of participants with newly occurring liver enzyme abnormalities occurring at any time post-baseline will be summarized by dose cohort and by overall.

4.11.4 Vital Signs, Physical Findings and Other Observations Related to Safety

Vital Signs

Oral, tympanic or temporal body temperature, respiratory rate, pulse, and systolic and diastolic blood pressure will be assessed.

Vital signs data will be listed by participant including changes from baseline. The baseline for the vital signs' measurements will be the measurement obtained prior to administration of IV of XTMAB-16.

Table 7 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.

Toxicity grading of vital signs will be summarized by dose cohort.

Descriptive statistics (n, mean, SD, median, minimum, maximum) for absolute values and changes from baseline will be presented by dose cohort.

ECG

Standard safety 12-lead ECGs will be performed as shown in the Schedule of Assessments.

The following ECG parameters will be recorded:

P wave, QRS complex, U wave, QRS duration, QT interval, QTcF, T wave, ST segment, RR interval, PR interval, and qualitative results.

The ECG will be evaluated by the Investigator as ‘Normal’, ‘Abnormal, NCS’ or ‘Abnormal, CS’.

All ECG parameters will be listed by participant for each dose cohort and time point including changes from baseline. The baseline for the ECG measurements will be obtained prior to administration of IV of XTMAB-16.

Descriptive statistics (n, mean, SD, median, lower quartile, upper quartile, minimum, maximum) for absolute values and changes from baseline will be presented by dose cohort and pooled placebo group. A categorical QTc analysis will also be performed.

A summary of the number and percentage of participants with QTcF intervals exceeding some predefined upper limits (e.g. >450ms, >480ms, >500ms for measured values as well as. >30ms, >60ms for changes from baseline) of ECG parameters will be displayed in a frequency table.

Mean QTcF values (±SD) over time per dose and pooled placebo will be presented graphically on Safety set.

If findings on telemetry are identified, a further concentration QT analysis (tie-matched QT and QTc analysis for XTMAB-16 and placebo) **may** be further evaluated. ER analysis consists of the following:

1. A linear mixed effects model with ΔQTcF as the dependent variable, drug plasma concentration as a continuous covariate, treatment (active or placebo) as categorical factor, and a random intercept for each participant. Note: concentration values are set to 0 for placebo participants.
2. The predicted mean ΔΔQTcF (placebo corrected, change from baseline) at the observed geometric mean Cmax (i.e., the product with the slope estimate treatment effect [active – placebo]) will be calculated. Two-sided 90% CIs of the estimate will be calculated using a bias-corrected nonparametric bootstrap with 1,000 resamples and participant as the unit of resampling. Note: Bootstrap is used to provide robust estimate for the 90% CI.
   Resampling will be done independently for the active and the placebo participants. For each resample, the model will be fitted and the predicted mean ΔΔQTcF will be computed at the geometric mean Cmax determined from the resampled data. The 90% CI will be determined from the distribution of resampled predicted values.
3. Decisions to classify the risk QTprolongation induced by XTMAB-16, the upper bound of the two-sided 90% CI for the ΔΔQTcF effect of XTMAB-16 as estimated by ER model should be <10ms at the observed geometric mean Cmax to exclude a risk QT prolongation induced by XTMAB-16. (reference: ICH E14 Guideline: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs Questions & Answers (R3))

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.)

Abnormal physical examination findings will be listed.

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.

Assessment of liver-related changes will be summarized.

4.11.5 Safety Monitoring (Independent Data Monitoring Committee [IDMC], Data Monitoring Committee [DMC], Data and Safety Monitoring Board [DSMB])

Not Applicable.

4.12 Other Analyses

4.12.1 Immunogenicity

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.
If ADA or nAb are detected, a summary table of PK parameter by ADA and nAb status (Positive or Negative) will be provided using PK analysis set.
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 cohort and Day.

4.12.2 Biomarker Analysis

Biomarker analysis of ACE, sIL-2R, IL-6, and sTNFα will be based on Biomarker Set.

All participants 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, participants being included in this population and having received only placebo will also be included as part of this data set.

Percent change from Baseline over time and total (absolute) change from Baseline will be analyzed.

4.12.2.1 Biomarker Concentration-Time Data

Biomarkers (ACE, sIL-2R, IL-6, and sTNFα) at each biomarker sampling times will be summarized with descriptive statistics (N, mean, SD, CV%, geometric mean, geometric CV%, median, minimum, and maximum) for treatment, day, and nominal timepoint.

For presentation in biomarker summary tables if less than 4 significant digits, all summary statistics will be tabulated to one more significant digit compared to the source data, otherwise up to a maximum of 4 significant digits, with exception of N, and n that will be presented as whole numbers, CV% and geometric CV% that will be presented to 1 decimal place.

To visualize the comparison between treatment, the following descriptive biomarker graphs will be generated. For each figure participants belonging to each category will be shown on the same plot with separate figures for each level of dose. Figures will be displayed in unique line and marker color, line style and marker for each plot in the graph. For all biomarker-time plots, linear scale will be used for both x-axis and y-axis. The following plots will be generated for each of biomarkers.

- Figure xx.1: Individual Biomarker-Time Profiles (Absolute change and percent change from Baseline) (Biomarker Set)
- Figure xx.2: Mean (± SD) Biomarker-Time Profiles (Absolute change and percent change from Baseline) by dose and placebo groups (Biomarker Set)

4.12.2.2 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.

Biomarker parameters will be provided by CPMS group. Biostatistics group will use this data for calculation of biomarker parameter summary statistics tables.

Biomarker parameters will be calculated by non-compartmental analysis methods from the biomarker-time data using Phoenix® WinNonlin® (Version 8.2) or higher following these guidelines:

- Actual sampling times relative to the start of infusion rather than nominal times will be used in the calculation of all derived biomarker parameters.
- There will be no imputation of missing data.

Biomarker parameters will be listed by treatment and subject for the Biomarker Set. Biomarker parameters will be summarized by different dose and placebo groups.

For presentation in biomarker parameter summary tables if less than 4 significant digits, all summary statistics will be tabulated to one more significant digit compared to the source data, otherwise up to a maximum of 4 significant digits, with exception of N, and n that will be presented as whole numbers, CV% and geometric CV% that will be presented to 1 decimal place.

4.13 Determination of Sample Size

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.

4.14 Changes in the Conduct of the Study or Planned Analysis

None.

5 REFERENCES

[1] SAS® Version 9.4 of the SAS System for Personal Computers. Copyright © 2002-2003. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.
[2] Phoenix®WinNonlin® Professional Software Version 8.2. https://www.certara.com

6 APPENDICES

6.1 Schedule of Assessments

Table 8 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.

Table 9 Grading of 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 reliver > 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 – 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 actual measurement.

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