Celerion Project No.: CA19214

Sponsor Project No.: 3G3-15-01

US PIND No.: 127850

A Phase 1, Single Ascending Dose, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Xisomab 3G3 in Healthy Adult Subjects

GCP Statement

This study is to be performed in full compliance with the protocol, Good Clinical Practices (GCP), and applicable regulatory requirements. All required study documentation will be archived as required by regulatory authorities.

Confidentiality Statement

1. PROTOCOL REVISION HISTORY

DATE/NAME	DESCRIPTION
06Nov2017 by Caroline Engel	Amendment 3, Final Protocol I. At the Sponsor request, exploratory analysis will be performed on leftover pharmacokinetic plasma samples. Hence the following sentence was added to Section 5 Synopsis under Pharmacokinetic Sample Collection and Section 11.2.1 Blood Sampling and Processing: "Additional analysis for exploratory purposes, including but not limited to factor XIa activity, will be performed on leftover plasma samples at the Sponsor's discretion." II. In addition, the serum chemistry tests scheduled 8 hours postdose will not be performed following an 8-hour fast as subjects will receive their lunch approximately 4 hours before. Therefore the following sections were updated (added wording in **bold**): 1. Section 6 Study Event Flow Chart (footnote h): "Samples for serum chemistry will be obtained following a fast of at least 8 hours **(except for the 8-hour time point)**, however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours before the serum chemistry sample is taken." 2. The first sentence in the last paragraph of Section 10.2.3.2 Meal Schedule: "Subjects will be required to fast for at least 8 hours before the clinical laboratory tests at screening and before the clinical laboratory tests at other scheduled times **(except for the 8-hour time point)**." 3. Section 11.1.5 Clinical Laboratory Tests (footnote *): "Serum chemistry tests will be performed after at least an 8-hour fast **(except for the 8-hour time point)**; however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours before the serum chemistry sample is taken" III. Severity grading scales to be used for adverse events (AEs) reporting will be based on detailed toxicity scales provided in the FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. Hence the table listing the general definition for rating severity of the AE

DATE/NAME	DESCRIPTION
06Nov2017 by Caroline Engel (Continued)	generated from the FDA toxicity grading scale provided in Section 11.1.9.3 Reporting will be applied only for AEs not identified in the guidance. Therefore the section 11.1.9.3 Reporting was updated as follow (added text in **bold**): "Severity of AE: **Severity rating used during the study will be based on the the toxicity grading scale tables present in the FDA (Center for Biologics Evaluation and Research) toxicity grading scale for healthy volunteers 4-point severity scale (Grade 1, 2, 3 and 4).**[3] The following definitions for rating severity will be used **for AEs not identified in the guidance**: (…)" IV. Formatting changes and typographical errors were corrected throughout the protocol.
10May2017 by Caroline Engel	Amendment 2, Final Protocol 1. At the Sponsor request a PT/INR sample was added on Day 4 of the study. Therefore, the following changes were made to reflect this addition: • Section 6 Study Event Flow Chart was updated to add an "X" on Day 4 for Coagulation (PT/INR) row. • To prevent confusion, the footnote "i" was removed from all the "X" between Day 2 and Day 29 in the Coagulation (PT/INR) row and added to "Coagulation (PT/INR)" in the Study Procedures column. • Table 2 was updated. The number of samples was updated to "at least 5" under Number of Time Points column and On-study coagulation (PT/INR only) row. 2. Celerion recently moved from the standard 4.5mL tube for coagulation to a new 3.5mL tube. Therefore Table 2 was updated accordingly to reflect that change. The total blood volume has decreased from 318.5 mL to 300.5 mL. 3. Formating changes were made throughout the protocol.
02May2017 by Caroline Engel 02May2017	Amendment 1, Final Protocol Based on FDA recommendations, the following changes were made to the protocol:

DATE/NAME	DESCRIPTION
by Caroline Engel (Continued) 02May2017	1. All subjects, regardless of their aPTT results, will be monitored until Day 29. Therefore, if aPTT value reaches ±10% of the baseline value or within the normal range by Day 29, the subject will return to the clinical research unit (CRU) for the FU visit on Day 36. If aPTT value does not reach ± 10% of the baseline value or within the normal range by Day 29, sampling will continue every 7 days (± 2 days) until the ± 10% of baseline value or the normal range is reached. Subjects will return for the FU visit (i.e., follow-up procedures and AE evaluation) 7 days (± 2 days) after aPTT value reaches ±10% of the baseline value or within the normal range. The protocol was updated throughout to reflect this change. 2. The dosing interval between the sentinel group and the remaining subjects was revised to at least 7 days in Cohort 1. The remaining subjects in Cohort 1 and all subjects in Cohorts 2-4 will be dosed at an interval of 24 hours between subjects. The protocol was updated throughout to reflect this change. 3. Section 10.2.3.3 was revised to clarify that the designated times for aPTT assessments are listed in the study events flow chart. 4. Subjects with normal renal and liver function, and normal coagulation parameters will be enrolled in this study. Therefore the following inclusion criteria were added to Section 10.3.2 Inclusion Criteria and Appendix 1 was added to list Celerion standards for normal limits of the listed laboratory tests: • Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), blood urea nitrogen (BUN), creatinine must be between the lower limit of normal (LLN; or up to 15% below LLN as not indicative of hepatic or renal disease in healthy subjects) and the upper limit of normal, inclusive, as indicated in Appendix 1 at screening and check-in. • aPTT, PT/INR, and platelets, must be within the limits of normal, inclusive, as indicated in Appendix 1 at screening and check-in. • Bleeding time must be between 2 to 8 minutes, inclusive, at check-in. 5. Up to 28 days of safety data will be used and reviewed for dose escalation decision instead of 7 days. As well, Section 10.4.1.4 Dose Escalation and Stopping Rules was updated to clarify that

DATE/NAME	DESCRIPTION
by Caroline Engel (Continued) 02May2017	all data from all subjects will be used and reviewed for dose escalation decision and a minimum of 4 subjects must complete the study (up to Day 29) before proceeding to the next higher dosing cohort. The second paragraph of Section 10.4.1.4 Dose Escalation and Stopping Rules was updated as follows (deleted text presented in strikethrough; added text presented in bold): "The SRC will review all pertinent blinded safety/tolerability data (e.g., physical examinations, ECGs, vital signs, clinical laboratory tests, and AEs) using all available data collected **from all subjects dosed** ~~to at least Day 8 for a minimum of 4 out of 5 subjects from~~ **in** the current cohort and from all subjects from previous cohorts **to base dose escalation decision. At least 4 out of 5 subjects from the current cohort must complete scheduled safety procedures up to Day 29** prior to the decision to ~~open~~ **proceed to** the next higher dosing cohort" 6. All SAEs, regardless of presumed relatedness to study drug, will be considered for dose escalation decisions, except those that are clearly and incontrovertibly due to extraneous causes. Therefore rules #3a in Section 10.4.1.4 Dose Escalation and Stopping Rules was updated as follows (deleted text presented in strikethrough; added text presented in bold): "At least 1 subject has a SAE or visit to the emergency room ~~deemed to be study drug related~~ **regardless of relatedness to the study drug, except SAEs that are clearly and incontrovertibly due to extraneous causes.**" In addition, the following changes were made: 7. Clinical laboratory tests were added 8 hour after dosing. Section 6 Study Event Flow Chart and Table 2 (in Section 11.4 Blood Volume for Study Assessments) were updated accordingly. 8. Section 8.4.2 Dose Selection was updated to add the following information (deleted text presented in strikethrough; added text presented in bold): "(…) Using the regulatory guidance for estimating a safe starting dose in humans, the maximum recommended starting dose (MRSD) based on the NOAEL from the toxicology studies with a **default safety** ~~correction~~ factor of 10 applied was determined to be 5 mg/kg. **The PAD determined by the non-GLP in vivo efficacy studies in baboons was 1 mg/kg and is,**

DATE/NAME	DESCRIPTION
by Caroline Engel (Continued)	**therefore, 5-fold lower than the MRSD based on the NOAEL. Dividing the PAD by a safety factor of 10 would provide a very conservative starting dose of 0.1 mg/kg.** ~~The MRSD based on the pharmacologically active dose from in vivo efficacy studies in baboons with a correction factor of 10 was determined to be 0.1 mg/kg~~. (…)" 9. In Section 14 Reference, reference #5 was removed since it is not referred to in the protocol. 10. Typographical and gramatical errors were corrected throughout the protocol. 11. Formating changes were made throughout the protocol.
03Mar2017 by Caroline Engel	Final Protocol for FDA submission

2. PRINCIPAL INVESTIGATOR AND SPONSOR – SIGNATORIES

A Phase 1, Single Ascending Dose, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Xisomab 3G3 in Healthy Adult Subjects

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5. SYNOPSIS

Compound	xisomab 3G3 (anti-FXI monoclonal antibody, IgG4)
	Active Ingredient: xisomab 3G3 (~15 mg/mL) [redacted]
Clinical Indication	Prevention and treatment of venous thrombosis and thromboembolism
Study Phase and Type	Phase 1, single ascending dose (SAD), first-in-human study
Study Objectives	The primary objective of the study is to assess the safety and tolerability of single intravenous (IV) doses of xisomab 3G3 when administered to healthy adult subjects. The secondary objectives of the study are as follows: 1. To assess the pharmacokinetics (PK) of single IV doses of xisomab 3G3 when administered to healthy adult subjects. 2. To assess the pharmacodynamics (PD) of single IV doses of xisomab 3G3 when administered to healthy adult subjects. The activated partial thromboplastin time (aPTT) will be used as a surrogate PD marker.
Study Design	This is a randomized, double-blind, placebo-controlled, SAD study conducted at one study center in the United States (US). Four (4) cohorts of either 6 subjects (Cohort 1 [4 active and 2 placebo]) or 5 subjects (Cohorts 2, 3, and 4 [4 active and 1 placebo]) are planned for evaluation. In each cohort, subjects will receive a single IV infusion of xisomab 3G3 or placebo. Subjects will participate in only one cohort. Safety (e.g., physical examinations, vital signs, electrocardiograms (ECGs), clinical laboratory tests, injection site reaction, immunogenicity, and adverse events [AEs]) will be assessed throughout the study; serial blood samples and urine samples will be collected for these assessments. Blood samples will also be collected for the PK (free xisomab 3G3) and PD (aPTT) assessments of xisomab 3G3 at scheduled time points as listed in the Study Events Flow Chart (Section 6) for at least 672 hours postdose. Following the 672-hour time point, sample collection for PK and PD assessments will continue every 7 days

	(± 2 days) until aPTT values return within ±10% of the baseline value or the normal range. Anti-drug antibodies (ADA) sample collection will be performed on Days 15 and 29 for all subjects. If aPTT values remain elevated past Day 29, an additional ADA sample collection will occur at the follow-up (FU) visit. Dose escalation to the next dose level (i.e., next cohort) will not take place until the Safety Review Committee (SRC) has determined that adequate safety and tolerability of xisomab 3G3 from the current and previous cohorts has been demonstrated to permit proceeding to the next cohort. Interim PK and PD analyses may be performed to reconsider the sampling time points as the study progresses and to guide the dose-escalation decision. Subjects for whom aPTT value reaches ±10% of the baseline value or within the normal range by Day 29, will return to the clinical research unit (CRU) for the FU visit on Day 36 to perform scheduled follow-up procedures and to determine if any AE has occurred since the last study visit. Subjects for whom aPTT did not reach ±10% of the baseline value or within the normal range on Day 29, will return every 7 days (±2 days) until aPTT reach ±10% of the baseline value or within the normal range and for the FU visit (i.e., follow-up procedures and AE evaluation) 7 days (±2 days) after it was reached. If aPTT values remain elevated past Day 29, an additional ADA sample collection will occur at the FU visit. Subjects who terminate the study early will be asked to continue aPTT monitoring as scheduled in the Study Events Flow Chart (Section 6) until it reaches ±10% of the baseline value or within the normal range. They will return to the CRU approximately 7 days (±2 days) after aPTT reaches ±10% of the baseline value or within normal range for the FU visit to perform scheduled follow-up procedures, and to determine if any AE has occurred since the last study visit. They will also be asked to return on Days 15 and 29 to collect the ADA samples.
Study Population	Subjects will be healthy male subjects and healthy female subjects of non-childbearing potential.
Number of Subjects	The study is planned to enroll up to 21 subjects in 4 cohorts. The first cohort will enroll 6 subjects; 4 subjects randomized to receive the active drug and 2 subjects to receive the placebo. The remaining 3 cohorts will enroll 5 subjects; 4 subjects randomized to receive the

	active drug and 1 subject to receive the placebo. In each cohort, at least 30% of the subjects must be of a race/ethnicity minority group. An attempt will be made to include at least 2 females per cohort. Two sentinel subjects will be dosed (one placebo, one active) in Cohort 1 and data will be collected through Day 8. The next subject in the cohort will be dosed after evaluation of the sentinel subjects' Day 8 safety data. Each subject following these sentinel subjects will be dosed with an interval of 24-hour between subjects. Subjects in Cohorts 2, 3, and 4 will be dosed at an interval of 24 hours between subjects. Additional subjects (N = 5 subjects per cohort; 4 active and 1 placebo) may be enrolled if it is deemed appropriate by the SRC to repeat a dose level or to study an interim dose level (lower than those planned) in a new cohort of subjects.
Duration of Participation for Subjects	The total planned duration of subject participation is up to 63 days from screening to follow-up, if aPTT values return within ±10% of the baseline value or the normal range by Day 29. This participation period could be prolonged if aPTT values did not reach ±10% of the baseline value or within the normal range by Day 29.
Study Products	Xisomab 3G3 will be supplied as sterile powder for injection via the IV route, upon reconstitution. Matching placebo will be supplied as sterile powder for injection via IV route, upon reconstitution. An unblinded pharmacist will be responsible for providing xisomab 3G3 or placebo to the blinded study personnel for IV infusion.
Planned Dose Levels	On Day 1, subjects in each cohort will receive a single hand pushed IV infusion of xisomab 3G3 or placebo on one occasion. Planned doses will be as follows: Cohort 1: 0.1 mg/kg xisomab 3G3 or matching placebo Cohort 2: 0.5 mg/kg xisomab 3G3 or matching placebo Cohort 3: 2 mg/kg xisomab 3G3 or matching placebo Cohort 4: 5 mg/kg xisomab 3G3 or matching placebo Dosing will not exceed 5 mg/kg without a protocol amendment.

Safety Assessments	Safety will be monitored through physical examinations, vital signs, ECGs, clinical laboratory tests (including, but not limited to, hematology, serum chemistry profile, coagulation, and urinalysis), injection site reaction, immunogenicity, and AEs.
Safety Analysis	The following analyses will be performed; however no formal inferential statistics will be done on safety assessments. The placebo subjects from all cohorts will be pooled into a single placebo group for all summaries and presentations. Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data. **Adverse Events:** AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities® (MedDRA®) available at Celerion. A by-subject AE data listing, including verbatim term, preferred term, treatment, severity, and relationship to drug, will be provided. The number of subjects experiencing treatment-emergent adverse events (TEAEs) and number of TEAEs will be summarized by treatment using frequency counts. Injection site reaction will be assessed. **Medical History and Physical Examination:** Medical history will be listed by subject. Changes in physical examinations will be described in the text of the final report. **Clinical Laboratory Results, Electrocardiograms, and Vital Signs Measurements:** All clinical laboratory results, 12-lead ECGs, vital signs measurements, and their change from baseline, will be summarized by treatment and time point of collection. A shift table describing out-of-normal range shifts will be provided for clinical laboratory results. **Concomitant Medications:** Concomitant medications will be listed by treatment. **Immunogenicity:** ADA detection will be reported and summarized descriptively.

Pharmacokinetic Sample Collection	Serial blood samples will be collected prior to and following the dose on Day 1 to determine the concentration of free xisomab 3G3 in plasma as indicated in the Study Events Flow Chart (Section 6). Additional analysis for exploratory purposes, including but not limited to factor XIa activity, will be performed on leftover plasma samples at the Sponsor's discretion. The sampling schedule may be modified based on the results from previous cohorts. Note: the sample times for PK collection are in relation to the start of infusion.
Pharmacokinetic Parameters and Analysis	The following non-compartmental PK parameters will be calculated for free xisomab 3G3 in plasma, as appropriate: $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, $AUC_{\%extrap}$, C_{max}, T_{max}, K_{el}, $T_{½}$, MRT, CL, and V_{ss}. Additional PK parameters may be calculated if deemed appropriate. PK parameters will be summarized by treatment using descriptive statistics.
Pharmacodynamic Assessment	Serial blood samples will be collected prior to and following the dose on Day 1 for aPTT as indicated in the Study Events Flow Chart (Section 6).
Pharmacodynamic Analysis	aPTT values will be listed and presented graphically. PD parameters may be calculated if deemed appropriate.

6. STUDY EVENTS FLOW CHART

Study Procedures [a]		**Study Days**																
Days →	**Screening** [b]	**-1**	**1**						**2**	**4**	**6**	**8**	**10**	**15**	**22**	**29**	**FU** [c]
Hours →		**C-I** [d]	**0**	**0.083**	**0.25**	**0.5**	**1**	**3**	**8**	**24**	**72**	**120**	**168**	**216**	**336**	**504**	**672**	
Administrative Procedures																		
Informed Consent	X																	
Inclusion/Exclusion Criteria	X	X																
Medical History	X																	
Safety Evaluations																		
Full Physical Examination [e]	X	X																
Abbreviated Physical Examination							X			X							X [f]	X
Height	X																	
Weight	X	X																
12-Lead Electrocardiogram	X		X [g]		X								X				X [f]	X
Vital Signs (HR, BP, RR, and T)	X		X [g]		X								X				X [f]	X
Hem, Serum Chem [h], and UA	X	X							X	X			X				X [f]	X
Coagulation (PT/INR) [i]	X	X					X			X	X		X				X [f]	X
Coagulation (aPTT)	X	X																X
Bleeding Time [j]		X	X [k]				X			X								
Serum Pregnancy Test (females only)	X	X																X
Serum FSH (postmenopausal females only)	X																	
Urine Alcohol/Drug Screen	X	X																
HIV/Hepatitis Screen	X																	
Adverse Events Monitoring		X																X
Concomitant Medication Monitoring	X	X																
Study Drug Administration / PK / PD / Immunogenicity																		
xisomab 3G3/Placebo Administration			X															
Blood for free xisomab 3G3 PK [l]			X [k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood for xisomab 3G3 PD (aPTT) [l]			X [k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood for Immunogenicity			X [k]												X		X	X [m]

Study Procedures [a]		**Study Days**																	
Days →	**Screening** [b]	**-1**	**1**							**2**	**4**	**6**	**8**	**10**	**15**	**22**	**29**	**FU** [c]
Hours →		**C-I** [d]	**0**	**0.083**	**0.25**	**0.5**	**1**	**3**	**8**	**24**	**72**	**120**	**168**	**216**	**336**	**504**	**672**	
Other Procedures																		
Injection Site Reaction			X [k]				X			X								
Confinement in the CRU [i]		X																
Visit and Return Visits [i]	X										X	X	X	X	X	X	X	

a: For details on Procedures, refer to Section 11.
b: Within 28 days prior to the study drug administration.
c: Subjects for whom aPTT value reaches ± 10% of the baseline value or within the normal range by Day 29, will return to the CRU for the FU visit on Day 36 to perform scheduled follow-up procedures, and to determine if any AE has occurred since the last study visit.

Subjects for whom aPTT did not reach ± 10% of the baseline value or within the normal range on Day 29, will return every 7 days (±2 days) until aPTT reach ±10% of the baseline value or within the normal range and for the FU visit (i.e., follow-up procedures and AE evaluation) 7 days (± 2 days) after it was reached.

Subjects who terminate the study early will be asked to continue aPTT monitoring as scheduled until it reaches ± 10% of the baseline value or within the normal range. They will return to the CRU approximately 7 days (± 2 days) after aPTT reaches ± 10% of the baseline value or within normal range for the FU visit to perform scheduled follow-up procedures, and to determine if any AE has occurred since the last study visit. They will also be asked to return on Days 15 and 29 to collect the ADA samples.
d: Subjects will be admitted to the CRU on Day -1, at the time indicated by the CRU.
e: Symptom-driven physical examination may be performed at other times, at the PI's or designee discretion.
f: To be performed on Day 29 or at early termination.
g: To be performed within 24 hours prior to dosing.
h: Samples for serum chemistry will be obtained following a fast of at least 8 hours (except for the 8-hour time point), however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours before the serum chemistry sample is taken.
i: If PT/INR values are ≤ 3.5 and judged not clinically significant by the PI or designee, the subject will be released from the CRU. Subject will need to return to the CRU at least 2 days after discharge to confirm these values.
j: Bleeding time will be performed on both subject's arm at each scheduled time point.
k: To be performed prior to dosing.
l: aPTT and free xisomab 3G3 blood samples will be collected for at least 672 hours and until aPTT values return within ± 10% of baseline value or the normal range. If by Day 29, aPTT has not returned to baseline or normal range, sampling will continue every 7 days (± 2 days) until the ± 10% of baseline value or the normal range was reached or, as per PI discretion, a maximum of ~500 mL of blood was collected from the subject. Subjects who terminate the study early will return every 7 days (± 2 days) for aPTT monitoring until aPTT values return within ± 10% of baseline value or the normal range.
m: An additional ADA sample will be collected at the FU visit only in the event that the FU visit occurs after Day 36.

Abbreviations: ADA = anti-drug antibodies, aPTT = Activated partial thromboplastin time, BP = Blood pressure, C-I = Check-in, Chem = Chemistry, CRU = Clinical research unit, FSH = Follicle-stimulating hormone, FU = Follow-up, Hem = Hematology, HIV = Human immunodeficiency virus, HR = Heart rate, INR = International normalized ratio, PD = Pharmacodynamic, PI = Principal Investigator, PK = Pharmacokinetics, PT = Prothrombin time, RR = Respiratory rate, T = Temperature, UA = Urinalysis.

7. ABBREVIATIONS

ADA	Anti-drug antibodies
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
$AUC_{\%extrap}$	Percent of $AUC_{0\text{-}inf}$ extrapolated
$AUC_{0\text{-}inf}$	Area under the concentration-time curve, from time 0 extrapolated to infinity
$AUC_{0\text{-}t}$	Area under the concentration-time curve, from time 0 to the last observed non-zero concentration (t)
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
BUN	Blood urea nitrogen
°C	Degrees Celsius
CFR	Code of Federal Regulations
Chem	Chemistry
CL	Apparent total plasma clearance
cm	Centimeter
C_{max}	Maximum observed concentration
CRF	Case report form
CRU	Clinical Research Unit
dL	Deciliter
ECG	Electrocardiogram
FDA	Unites States Foods and Drug Administration
FIX	Factor IX
FSH	Follicle-stimulating hormone
FU	Follow-up

FXI	Factor XI
FXIa	Activated factor XI
FXII	Factor XII
FXIIa	Activated factor XII
g	Gram
GCP	Good clinical practice
GLP	Good laboratory practice
h	Hour
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IL	Interleukin
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous
K_{el}	Apparent terminal elimination rate constant
kg	Kilogram
L	Liter
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
µg	Microgram
m^2	Meters squared
MABEL	Minimum anticipated biological effect level
MedDRA®	Medical Dictionary for Regulatory Activities®
mg	Milligram
mL	Milliliter

mmHg	Millimeter of mercury
MRSD	Maximum recommended starting dose
MRT	Mean residence time
msec	Millisecond
MTD	Maximum tolerated dose
No.	Number
NOAEL	No observed adverse effect level
oz	Ounce
PBMC	Peripheral blood mononuclear cells
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetics
PT	Prothrombin time
QA	Quality assurance
QTcF	Friderica's correction
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SOP	Standard operating procedure
SRC	Safety review committee
$T_{½}$	Apparent terminal elimination half-life
TEAE	Treatment-emergent adverse event
T_{max}	Time to reach maximum observed concentration
UA	Urinalysis
US	Unites States of America
USA	United States of America
V_d	Apparent volume of distribution
V_{ss}	Total apparent volume of distribution following single IV dose

8. BACKGROUND AND RATIONALE

8.1 Introduction

This study is being conducted as the first in a series of studies for the clinical development of xisomab 3G3. The trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and applicable regulatory requirements. The subject population will be comprised of healthy adult male and/or female subjects.

A brief overview of available information regarding xisomab 3G3 follows below. Details can be found in the xisomab 3G3 Investigator's Brochure (IB). [1]

8.2 Background

Xisomab 3G3 is a novel, injectable, therapeutic monoclonal antibody that inhibits activation of the contact (intrinsic) pathway of coagulation and is intended to address the problem of dose limiting bleeding side effects of current antithrombotic agents. Xisomab 3G3 was developed by Aronora, Inc. and the current formulation is intended for IV administration. The proposed indications for xisomab 3G3 include prevention or treatment of thrombotic and thromboembolic diseases, such as venous thrombosis and thromboembolism.

Aronora, Inc. has conducted a comprehensive nonclinical pharmacology and toxicology program in support of clinical development of xisomab 3G3. Experimental evidence suggests that contact pathway activation promotes thrombosis, but it has no known role in normal hemostasis. Contact pathway activation is initiated by auto-activation of coagulation Factor XII (FXII) on negatively charged surfaces. Activated FXII (FXIIa) then activates coagulation Factor XI (FXI), which then activates coagulation Factor IX (FIX) and ultimately leads to generation of the procoagulant enzyme thrombin from prothrombin. The therapeutic monoclonal antibody xisomab 3G3 binds the apple 2 domain of FXI and therefore interferes with the activation of FXI by FXIIa. Importantly, this interaction selectively prevents activation of FXI by FXIIa without interfering with the vasoregulatory activities of FXIIa or the hemostatic feedback activation of FXI by thrombin, or other mechanisms, nor does it interfere with the catalytic activity of activated FXI (FXIa) on its hemostatic substrates. Because FXIIa does not contribute to the hemostasis of mammalian species, and activation of FXI by FXIIa is a pathological event that appears to promote thrombosis in experimental animals, inhibition of FXI activation by FXIIa using xisomab 3G3 is expected to be a safe and effective antithrombotic intervention in humans who are at risk or have developed thrombosis.

The goal of xisomab 3G3 treatment is to achieve safe anticoagulation for several days with a single dose. A single dose of xisomab 3G3 demonstrated potent and sustained antithrombotic effects in both mice and nonhuman primate models, and showed no toxicity at and above saturating doses in nonclinical Good laboratory Practice (GLP) toxicity studies in rats and cynomolgus monkeys. Saturation of binding to the molecular target and the maximum FXI inhibitory effect is achieved at a relatively low dose of xisomab 3G3 because FXI circulates at a low plasma concentration (3 to 10 mg/L), and the antibody has high affinity toward FXI. The effect of increasing the dose above the saturating level results in prolongation of

anticoagulation in a dose-dependent manner. Since there has been no observed toxicity associated with a dose more than 50-fold over the predicted effective target dose in humans as determined by GLP toxicity studies in both rats and nonhuman primates, the therapeutic index is expected to be very high.

8.3 Nonclinical Studies

8.3.1 Pharmacology

Inhibition of the contact pathway of coagulation by xisomab 3G3 or its murine precursor, xisomab 14E11, is antithrombotic as demonstrated by both in vitro and in vivo aPTT prolongation and in several experimental animal models of thrombosis, including a mouse model of $FeCl_3$-induced arterial thrombosis (Study No. AB023.4), a mouse model of sepsis (Study No. AB022.4), and a well-established model of thrombosis in baboons (Study No. AB023.5). Importantly, while treatment with xisomab 3G3 or 14E11 attenuated thrombosis in these experimental models of thrombosis, no demonstrable effect on hemostasis was observed. These data suggest that in contrast to currently marketed antithrombotics that target elements of the coagulation cascade important for both thrombosis and hemostasis, xisomab 3G3 is designed to selectively inhibit thrombosis without increasing risk of bleeding side effects.

8.3.2 Pharmacokinetics

Pharmacokinetics were evaluated in a non-GLP study in baboons (Papio Anubis) in which 1 mg/kg of xisomab 3G3 was administered by IV injection and free xisomab 3G3 plasma concentration was measured over time. Non-compartmental analysis of the xisomab 3G3 plasma concentration versus time curve revealed the maximal plasma concentrations normalized to dose (C_{max}/Dose) was 19.66 ± 0.56 L/kg, the area under the concentration time curve from time 0 to the last time point measured post-dose normalized to dose ($AUC_{0\text{-}xh}$/Dose) was 1594 ± 82 kg x h/L, and the apparent volume of distribution (V_d) was 0.050 ± 0.0012 L/kg. Group mean terminal elimination half-lives ($T_{½}$) ranged from 45 to 75 hours and the mean residence time (MRT) ranged from 88 to 110 hours in baboons after a 1 mg/kg IV injection.

In addition, toxicokinetics were evaluated as part of the pivotal toxicity studies in cynomolgus monkey and Sprague Dawley rats. In both studies, IV doses of 0, 2, 10, and 50 mg/kg of xisomab 3G3 were administered by IV bolus injection. All animals except controls showed systemic exposure to xisomab 3G3 following single IV dose. IV infusions of xisomab 3G3 in cynomolgus monkeys resulted in peak free xisomab 3G3 plasma concentrations at the first or second time point evaluated, approximately 0.5 - 3 hours following administration. Maximum concentrations remained generally sustained and therefore the terminal elimination phase was not well characterized for most profiles. In the absence of the recovery data for the main study animals, the terminal elimination phase could only be estimated with confidence for one male who received 10 mg/kg, with $T_{½}$, CL and V_d of 31.9 hours, 0.513 mL/h/kg, and 23.6 mL/kg, respectively. Inclusion of the recovery animals (n = 2/sex/group) for all dose levels allowed for better characterization of the terminal elimination phase, however, it could only be estimated for six out of twelve

recovery animals. Consequently, individual $T_{½}$ were longer and ranged from 61.4 to 248 hours. Individual CL and V_d were estimated between 0.142 and 0.535 mL/h/kg and 34.0 and 57.8 mL/kg, respectively.

IV infusions of xisomab 3G3 in rats resulted in peak xisomab 3G3 plasma concentrations at the first or second time point evaluated, approximately 0.5 - 3 hours following administration. The terminal elimination phase was only characterized for the males and females at the 50 mg/kg dose level, as the terminal elimination phase for the 2 and 10 mg/kg dose levels was not reported due to either a coefficient of determination less than 0.800 or the extrapolation of the AUC to infinity represented more than 20% of the total area. The $T_{½}$ for the males and females at the 50 mg/kg dose level was 155 hours and 185 hours respectively. The average volume of distribution (V_d) was 45.2 mL/kg and 45.3 mL/kg for the males respectively and the clearance (CL) was 0.202 and 0170 mL/h/kg for the males and females respectively.

8.3.3 Toxicology

The safety and toxicity profile of xisomab 3G3 was evaluated in two, GLP, single dose acute, toxicity studies in Sprague Dawley rats and cynomolgus monkeys. In both studies, a single dose of xisomab 3G3 was administered intravenously at doses of 0, 2, 10 and 50 mg/kg and animals were evaluated for 3 days (main group) and 28 days (recovery group) after dosing. Xisomab 3G3 was well tolerated in both species and no xisomab 3G3-related AEs were observed. An expected aPTT prolongation was observed in all groups dosed with xisomab 3G3, and the duration of effect was dose dependent. In the cynomolgus monkey study, there was no difference in aPTT prolongation between males and females. The prolonged aPTT was first observed 30 minutes after dosing (the first time point evaluated) and persisted until 336 hours postdose (Day 15) at 2 mg/kg and 672 hours postdose (Day 29) at 10 and 50 mg/kg. Similarly, in the Sprague Dawley rats study, prolonged aPTT was first observed at 30 minutes post-dose (the first time point evaluated) and was generally of similar magnitude across the dose groups and genders; the duration of the effect increased with increasing dose. The No Observed Adverse Effect Levels (NOAEL) for both studies was determined to be 50 mg/kg. In addition to the toxicity studies, a GLP tissue cross reactivity study was performed in a panel of human tissue to assess potential cross-reactivity of xisomab 3G3. No xisomab 3G3-related staining was observed in any of the human tissue samples (36 tissue types from 3 normal healthy donors). Cytokine release assays performed in peripheral blood mononuclear cells (PBMCs) from 10 healthy donors revealed that xisomab 3G3, presented in three different stimulation formats, did not stimulate the release of interleukin (IL)-2, IL-4, IL-6, IL-10, tumor necrosis factor alpha or interferon gamma from PBMCs of any of the donors.

8.4 Rationale

8.4.1 Purpose of the Study

This clinical trial will be a SAD study of xisomab 3G3 administered as an IV infusion. When developing new drugs for clinical indications, it is necessary to collect data on the safety, tolerability, and PK in order to support further development of the compound as a useful clinical candidate. This study will establish safety and tolerability profiles for xisomab 3G3 and will allow identifications of recommended dose levels and dose intervals in Phase 2 and subsequent studies.

8.4.2 Dose Selection

Xisomab 3G3 appeared well tolerated in a panel of standard animal toxicology studies. Since this is the initial study in humans, the initial dose of xisomab 3G3 has been justified conservatively according to the US Food and Drug Administration (FDA) guidance document "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers". [2]

The proposed clinical starting dose of 0.1 mg/kg was estimated based on the NOAEL determined by the toxicity studies, the pharmacologically active dose (PAD) from the non-GLP in vivo efficacy studies in baboons, in vitro aPTT studies in pooled human plasma, and an understanding of the mechanism of action of xisomab 3G3 and its target, FXI. As recommended by the Guidance, [2] scaling based on body weight rather than body surface area will be used because the NOAEL determined in both the rat and nonhuman primate GLP toxicity studies occur at the same mg/kg dose and xisomab 3G3 is a monoclonal antibody to be administered intravascularly whose molecular weight is greater than 100,000 Daltons. [2] On the basis of no adverse effects noted in the toxicity studies, the NOAEL was determined to be 50 mg/kg in both species. Using the regulatory guidance for estimating a safe starting dose in humans, the maximum recommended starting dose (MRSD) based on the NOAEL from the toxicology studies with a default safety factor of 10 applied was determined to be 5 mg/kg. The PAD determined by the non-GLP in vivo efficacy studies in baboons was 1 mg/kg and is, therefore, 5-fold lower than the MRSD based on the NOAEL. Dividing the PAD by a safety factor of 10 would provide a very conservative starting dose of 0.1 mg/kg. The selection of 0.1 mg/kg for the first in human starting dose is further supported when using the minimum anticipated biological effect level (MABEL) to select a starting dose. Using in vitro aPTT data from pooled human plasma in which the EC_{10} was calculated to be the equivalent of 0.11 mg/kg and knowledge of the xisomab 3G3 mechanism of action, the MABEL is estimated to be approximately 0.1 mg/kg. This dose is anticipated to produce a minimal biological effect in most human subjects.

The expected maximum level of anticoagulation is estimated to be achieved at or below a dose of 1 mg/kg based on the effect of xisomab 3G3 or its murine precursor, xisomab 14E11, on the contact pathway of coagulation as demonstrated by both in vitro and in vivo aPTT prolongation in pooled human plasma (Study No. AB023.1) and in several experimental animal models of thrombosis, including a mouse model of $FeCl_3$-induced arterial thrombosis (Study No. AB023.4), a mouse model of sepsis (Study No. AB022.4), and a well-established

model of thrombosis in baboons (Study No. AB023.5).

The doses will be escalated until a dose of 5 mg/kg is reached, in order to provide a broad range of doses available for the subsequent studies patients with thrombotic disease and maintain a safety margin of 10-fold below the NOAEL determined in both pivotal GLP toxicity studies.

Therefore, the present first-in-human dose escalation study will initiate single doses at 0.1 mg/kg and may escalate doses up to 5 mg/kg depending on the safety and dose tolerance parameters observed at each dose level during the study. Dosing will not exceed 5 mg/kg without a protocol amendment.

8.5 Risk/Benefit

The safety monitoring practices employed by this protocol (e.g., physical examination, vital signs, 12-lead ECG, hematology, serum chemistry, urinalysis, coagulation, injection site reaction monitoring, and AE questioning) are adequate to protect the subjects' safety and should detect all expected TEAEs.

As there is a potential to develop an immune response to a biologic agent, immunogenicity will be assessed in this study.

The approximate volume of blood planned for collection from each subject over the course of the study (see Section 11.4), presents no undue risk to the subjects nor does the possibility of collection (for wasting to ensure clean sample) of additional blood in the event an indwelling cannula is utilized and the possibility of additional blood for recheck of safety labs if deemed necessary by the PI or designee.

There will be no direct health benefit for trial participants from receipt of study drug. An indirect health benefit to the healthy subjects enrolled in this trial is the free medical tests received at screening and during the study.

9. STUDY OBJECTIVES AND ENDPOINTS

9.1 Study Objectives

The primary objective of the study is to assess the safety and tolerability of single IV doses of xisomab 3G3 when administered to healthy adult subjects.

The secondary objectives of the study are as follows:

1. To assess the PK of single IV doses of xisomab 3G3 when administered to healthy adult subjects.

2. To assess the PD of single IV doses of xisomab 3G3 when administered to healthy adult subjects. The aPTT will be used as a surrogate PD marker.

9.2 Study Endpoints

The primary endpoints of the study will be the number and severity of TEAEs following single doses of xisomab 3G3 and placebo.

The secondary endpoints are as follows:

1. The following PK parameters of free xisomab 3G3 in plasma following single IV dose, will be calculated, as appropriate: $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, $AUC_{\%extrap}$, C_{max}, T_{max}, K_{el}, $T_{½}$, MRT, CL, and V_{ss}.

2. aPTT values will be listed and presented graphically. PD parameters for aPTT following single IV doses of xisomab 3G3 may be calculated if deemed appropriate.

10. INVESTIGATIONAL PLAN

10.1 Overall Study Design and Plan

This is a randomized, double-blind, placebo-controlled, SAD study conducted at one study center in the US.

Four (4) cohorts of either 6 subjects (Cohort 1 [4 active and 2 placebo]) or 5 subjects (Cohorts 2, 3, and 4 [4 active and 1 placebo]) are planned for evaluation. In each cohort, subjects will receive a single IV infusion of xisomab 3G3 or placebo. Subjects will participate in only one cohort.

Safety (e.g., physical examinations, vital signs, ECGs, clinical laboratory tests, injection site reaction, immunogenicity, and AEs) will be assessed throughout the study; serial blood samples and urine samples will be collected for these assessments.

Blood samples will also be collected for the PK (free xisomab 3G3) and PD (aPTT) assessments of xisomab 3G3 at scheduled time points as listed in the Study Events Flow Chart (Section 6) for at least 672 hours postdose. Following the 672-hour time point, sample collection for PK and PD assessments will continue every 7 days (± 2 days) until aPTT values return within ±10% of the baseline value or the normal range.

ADA sample collection will be performed on Days 15 and 29 for all subjects. If aPTT values remain elevated past Day 29, an additional ADA sample collection will occur at the FU visit.

Dose escalation to the next dose level (i.e., next cohort) will not take place until the SRC has determined that adequate safety and tolerability of xisomab 3G3 from the current and previous cohorts has been demonstrated to permit proceeding to the next cohort.

Interim PK and PD analyses may be performed to reconsider the sampling time points as the study progresses and to guide the dose-escalation decision.

See the planned dose escalations in Section 10.4.1.2.

10.1.1 Confinement, Return Visits, and Follow-Up

Subjects will be housed on Day -1, at the time indicated by the CRU, until after the 24-hour blood draw and/or study procedures. Subjects will only be discharged if the prothrombin time (PT)/international normalized ratio (INR) values are ≤ 3.5 and judged not clinically significant by the PI or designee. Subject will need to return to the CRU at least 2 days after discharge to confirm the PT/INR values.

Subjects will return for study procedures as indicated in the Study Events Flow Chart (Section 6). At all times, a subject may be required to remain at the CRU for longer at the discretion of the PI or designee.

Subjects for whom aPTT value reaches ±10% of the baseline value or within the normal range by Day 29, will return to the CRU for the FU visit on Day 36 to perform scheduled

follow-up procedures and to determine if any AE has occurred since the last study visit.

Subjects for whom aPTT did not reach ±10% of the baseline value or within the normal range on Day 29, will return every 7 days (±2 days) until aPTT reach ±10% of the baseline value or within the normal range and for the FU visit (i.e., follow-up procedures and AE evaluation) 7 days (±2 days) after it was reached. If aPTT values remain elevated past Day 29, an additional ADA sample collection will occur at the FU visit.

Subjects who terminate the study early will be asked to continue aPTT monitoring as scheduled in the Study Events Flow Chart (Section 6) until it reaches ±10% of the baseline value or within the normal range. They will return to the CRU approximately 7 days (±2 days) after aPTT reaches ± 10% of the baseline value or within normal range for the FU visit to perform scheduled follow-up procedures and to determine if any AE has occurred since the last study visit. They will also be asked to return on Days 15 and 29 to collect the ADA samples.

10.1.2 Study Duration

The total planned duration of subject participation is up to 63 days from screening to follow-up, if aPTT value returns within ±10% of the baseline value or the normal range by Day 29. This participation period could be prolonged if aPTT values did not reach ±10% of the baseline value or within the normal range by Day 29.

10.2 Study Conduct

Please see the Study Events Flow Chart for a summary of the schedule of study participation and procedures in Section 6.

10.2.1 Screening

Screening will begin within 28 days prior to dosing. Informed consent will be obtained at screening (see Section 13.1.3). Subjects will have to meet all eligibility criteria before being enrolled in the study (see Section 10.3). Subjects will be informed of the study restrictions (see Section 10.3.5).

The following will be recorded at screening: medical history and demographic data, including name, sex, age, race, ethnicity, body weight (kg), height (cm), body mass index (BMI) (kg/m^2), and history of alcohol and tobacco use.

Screening procedures are listed in the Study Events Flow Chart Section 6.

10.2.2 Check-in Procedures (Day -1)

At check-in (Day -1), subjects will return to the CRU, and those subjects who satisfy all of the inclusion criteria and none of the exclusion criteria will qualify and be eligible for randomization. A check-in questionnaire will be reviewed for each subject to ensure that subjects remain eligible for the study since screening. Questions will focus on inclusion and exclusion criteria and on study restrictions.

Check-in procedures are listed in the Study Events Flow Chart (see Section 6).

10.2.3 Treatment Period (Day 1 to Day 29)

10.2.3.1 Single-dose Administration (Day 1) and Study Procedures (Days 1 to 29)

On the morning of Day 1, predose evaluations will be obtained.

Subjects will receive a single IV infusion dose of the assigned formulation (xisomab 3G3 or placebo) on the morning of Day 1. See Section 10.4.1 and Section 10.4.3.

Safety and tolerability will be monitored throughout the treatment period as listed in the Study Events Flow Chart (see Section 6).

Blood samples for PK and PD assessments (see Section 11.2.1 and Section 11.3) will be collected at the time points listed in the Study Events Flow Chart (see Section 6), for at least 672 hours postdose. Following the 672-hour time point, sample collection for PK and PD assessments will continue every 7 days (± 2 days) until aPTT values return within ±10% of the baseline value or the normal range, as indicated in in the Study Events Flow Chart (see Section 6). ADA sample collection will be performed on Days 15 and 29 for all subjects.

10.2.3.2 Meal Schedule

Water will be allowed ad libitum at all times. Other fluids may be given as part of meals and snacks but will be restricted at all other times throughout the confinement period.

At the CRU, standard meals and snacks will be provided at appropriate times. When confined in the CRU, subjects will be required to fast from all food and drink except water between meals and snacks.

Each meal and/or snack served at the CRU will be standardized and will be similar in caloric content and composition. The same menu and meal schedule will be administered uniformly for all subjects for all cohorts.

Subjects will be required to fast for at least 8 hours before the clinical laboratory tests at screening and before the clinical laboratory tests at other scheduled times (except for the 8-hour time point). However, in case of dropouts or rechecks, subjects may not have fasted for 8 hours before the serum chemistry sample is taken.

10.2.3.3 Day 29 Study Procedures

Before leaving the CRU facility on Day 29, all subjects will undergo all study procedures listed on Day 29 in the Study Events Flow Chart (see Section 6). In the event that aPTT values did not return within ±10% of the baseline value or the normal range, sampling will continue every 7 days (±2 days) , as indicated in in the Study Events Flow Chart (see Section 6), until ±10% of the baseline value or the normal range is reached.

10.2.4 Follow-up Visit

Subjects for whom aPTT value reaches ±10% of the baseline value or within the normal range by Day 29 will return to the CRU for the FU visit on Day 36 to perform scheduled follow-up procedures and to determine if any AE has occurred since the last study visit.

Subjects for whom aPTT did not reach ±10% of the baseline value or within the normal range on Day 29, will return every 7 days (±2 days) until aPTT reach ±10% of the baseline value or within the normal range and for the FU visit (i.e., follow-up procedures and AE evaluation) 7 days (±2 days) after it was reached. If aPTT values remain elevated past Day 29, an additional ADA sample collection will occur at the FU visit.

Subjects who terminate the study early will be asked to continue aPTT monitoring as scheduled in the Study Events Flow Chart (Section 6) until it reaches ±10% of the baseline value or within the normal range. They will return to the CRU approximately 7 days (±2 days) after aPTT reaches ±10% of the baseline value or within normal range for the FU visit to perform scheduled follow-up procedures, and to determine if any AE has occurred since the last study visit. They will also be asked to return on Days 15 and 29 to collect the ADA samples.

The follow-up procedures are listed in the Study Events Flow Chart (see Section 6).

10.2.5 Scheduled End of Study

The end of the study is scheduled after completion of the evaluations in the 4 cohorts or after dose-limiting clinical safety endpoints have been reached to preclude further increases of dose.

10.3 Selection of Study Population

10.3.1 Number of Subjects

The study is planned to enroll up to 21 subjects in 4 cohorts. The first cohort will enroll 6 subjects; 4 subjects randomized to receive the active drug and 2 subjects to receive the placebo. The remaining 3 cohorts will enroll 5 subjects; 4 subjects randomized to receive the active drug and 1 subject to receive the placebo per the randomization. In each cohort, at least 30% of the subjects must be of a race/ethnicity minority group. An attempt will be made to include at least 2 females per cohort.

Two sentinel subjects will be dosed (one placebo, one active) in Cohort 1 and data will be collected through Day 8 as described in the Study Events Flow Chart (Section 6). The next subject in the cohort will be dosed after evaluation of the sentinel subjects' Day 8 safety data. Each subject following these sentinel subjects will be dosed with an interval of 24-hour between subjects

Subjects in Cohorts 2, 3, and 4 will be dosed at an interval of 24 hours between subjects.

Additional subjects (N = 5 subjects per cohort; 4 active and 1 placebo) may be enrolled if it is deemed appropriate by the SRC to repeat a dose level or to study an interim dose level (lower than those planned) in a new cohort of subjects.

10.3.2 Inclusion Criteria

Subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study, unless otherwise specified:

1. Healthy adult male and/or female (non-childbearing potential only), 18 to 48 years of age, inclusive, at screening.

2. Continuous non-smoker who has not used nicotine-containing products for at least 3 months prior to dosing and throughout the study.

3. Body mass index (BMI) ≥ 19 and ≤ 29.0 (kg/m^2) and weight between 50 and 125 kg (inclusive) at screening.

4. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs or ECGs, as deemed by the PI or designee.

5. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), blood urea nitrogen (BUN), creatinine must be between the lower limit of normal (LLN; or up to 15% below LLN as not indicative of hepatic or renal disease in healthy subjects) and the upper limit of normal, inclusive, as indicated in Appendix 1 at screening and check-in.

6. aPTT, PT/INR, and platelets, must be within the limits of normal, inclusive, as indicated in Appendix 1 at screening and check-in.

7. Bleeding time must be between 2 to 8 minutes, inclusive, at check-in.

8. For a female of non-childbearing potential: must have undergone one of the following sterilization procedures at least 6 months prior to dosing:

   - hysteroscopic sterilization;
   - bilateral tubal ligation or bilateral salpingectomy;
   - hysterectomy;
   - bilateral oophorectomy;

   or be postmenopausal with amenorrhea for at least 1 year prior to dosing and follicle-stimulating hormone (FSH) serum levels consistent with postmenopausal status as per PI or designee judgment.

9. A non-vasectomized male subject whose sexual partner is sterile or was advised to use one of the following during the course of the study (or prior to study as specified) and for 90 days following dosing:

   - Abstain from sexual intercourse;

- An intrauterine device with spermicide;
- A physical barrier method (e.g., male or female condom, contraceptive sponge, diaphragm, cervical cap) with spermicide;
- An intravaginal system (e.g., NuvaRing®) for at least 3 months prior to dosing;
- An oral, implantable, transdermal, or injectable hormonal contraceptive for at least 3 months prior to dosing.

No restrictions are required for a vasectomized male provided his vasectomy has been performed 4 months or more prior to dosing. A male who has been vasectomized less than 4 months prior to dosing must follow the same restrictions as a non-vasectomized male.

10. If male, must agree to not donate sperm from dosing until 90 days after dosing.

11. Understands the study procedures in the informed consent form (ICF), and be willing and able to comply with the protocol.

10.3.3 Exclusion Criteria

Subjects will be excluded from the study if there is evidence of any of the following criteria at screening or check-in, as appropriate.

1. Subject is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.

2. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the PI or designee.

3. History of any illness that, in the opinion of the PI or designee, might confound the results of the study or poses an additional risk to the subject by their participation in the study.

4. History or presence of drug abuse within the last 2 years prior to dosing.

5. History of alcoholism within the last 2 years prior to dosing or a current history of imbibing 3 or more units of alcohol per day (1 unit is equivalent to 150 mL of wine or 360 mL of beer or 45 mL of 45% alcohol).

6. History or presence of hypersensitivity or idiosyncratic reaction to the study drug, any ingredients of the study drug, or related compounds.

7. History of a clinically significant allergy of any kind including a history of allergic or hypersensitivity reactions to any drugs.

8. History or presence of:

    - Bleeding disorder(s) and/or at risk of bleeding, including relevant familial history;
    - Clinically significant anemia, in the opinion of the PI or designee;
    - Thromboembolic disease;
    - Bleeding in the gastrointestinal tract or central nervous system.

9. Allergy to rodents.

10. Had a minor surgery or major physical injury less than 4 weeks or major surgery less than 12 weeks prior to screening.

11. Was hospitalized within 2 months of dosing, unless deemed acceptable by the PI or designee.

12. Female subjects of childbearing potential.

13. Female subjects who are pregnant or lactating.

14. Positive urine drug or alcohol results at screening or check-in.

15. Positive results at screening for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C antibodies (HCV).

16. Seated blood pressure is less than 90/40 mmHg or greater than 140/90 mmHg at screening.

17. Seated heart rate is lower than 40 bpm or higher than 100 bpm at screening.

18. QTcF interval is >450 msec (males) or >460 msec (females) or has ECG findings deemed abnormal with clinical significance by the PI or designee at screening.

19. Hemoglobin value of less than 11.5 g/dL for females and 13.0 g/dL for males, at screening or check-in.

20. Unable to refrain from or anticipates the use of:

    - Any prescription medications, non-prescription medications, herbal remedies, or vitamin supplements beginning approximately 14 days prior to dosing and throughout the study. Acetaminophen (up to 2 g per 24 hour period) may be permitted during the study and will be documented.
    - Any anticoagulants (i.e., warfarin, Low Molecular Weight Heparin), coagulants, anti-platelet (e.g., clopidogrel), nonsteroidal anti-inflammatory drugs and/or

acetylsalicylic acid beginning approximately 28 days prior to dosing and throughout the study. Appropriate sources will be consulted by the PI or designee to confirm lack of PK/PD interaction with study drug.

- Any investigational drugs or biologics beginning approximately 30 days prior to dosing and throughout the study.

- Any biologics developed from chinese hamster ovary cell cultures in their life time.

21. Has been on a diet incompatible with the on-study diet, in the opinion of the PI or designee, within the 28 days prior to dosing and throughout the study.

22. Donation of blood or significant blood loss within 56 days prior to dosing.

23. Plasma donation within 7 days prior to dosing.

24. Strenuous exercise/physical activity which could cause muscle aches or injury, including contact sports at any time from 72 hours before dosing until completion of the study.

25. Participation in another clinical study within 30 days prior to dosing. The 30-day window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of the current study.

26. Presence of any scars, or tattoos which may obscure the injection site, as deemed by PI or designee.

27. Any condition or circumstance, in the opinion of the PI or designee, which may make the subject unlikely to complete the study or comply with study procedures and requirements, or may pose a risk to the subject's safety.

10.3.4 Early Termination of Subjects from the Study

Subject participation in this trial may be discontinued for any of the following reasons:

1. Occurrence of any medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the protocol.

2. Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the PI that continued participation is not in the best interest of the subject.

3. Subject's decision to withdraw.

4. Requirement of prohibited concomitant medication.

5. Subject failure to comply with protocol requirements or study related procedures.

6. Termination of the study by the Sponsor, FDA, Celerion, SRC, or other regulatory authorities.

The clinical report will include reason(s) for subject withdrawals as well as details relevant to the subject withdrawal. If a subject is withdrawn from the trial prior to study completion, the subject will undergo all procedures scheduled for early termination as the situation allows (see Section 10.2.3.3). Any subject withdrawn due to an AE (whether serious or non-serious) or clinically significant abnormal laboratory test values will be evaluated by the PI or a monitoring physician and will be treated and/or followed up until the symptoms or values return to normal or acceptable levels, as judged by the PI or designee.

Subjects withdrawn may be replaced at the Sponsor's discretion.

10.3.5 Study Restrictions

10.3.5.1 Prohibitions and Concomitant Therapy

Consumption of foods and beverages containing the following substances will be prohibited as indicated:

- Xanthines/caffeine: 48 hours before dosing and throughout the period of sample collection (small amounts of caffeine derived from normal foodstuffs e.g., 250 mL/8 oz. decaffeinated coffee or other decaffeinated beverage, per day, with the exception of espresso; 45 g/1.5 oz chocolate bar, per day, would not be considered a deviation to this restriction)
- Alcohol: 48 hours before dosing and throughout the period of sample collection;

Concomitant therapies will be prohibited as listed in the exclusion criteria in Section 10.3.3.

During the study, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the PI or designee.

If deviations occur, the PI or designee will decide on a case-by-case basis whether the subject may continue participation in the study based on the time the study medication was administered and its pharmacology.

All medications taken by subjects during the course of the study will be recorded.

10.3.5.2 Activity

Subjects will remain ambulatory or seated upright for the first 4 hours following study medication administration, except when they are supine or semi-reclined for study procedures. However, should AEs occur at any time, subjects may be placed in an appropriate position or will be permitted to lie down on their side.

Subjects will be instructed to refrain from strenuous exercise/physical activity which could cause muscle aches or injury, including contact sports at any time from 72 hours before to dosing until completion of the study.

10.4 Treatments

10.4.1 Treatments Administered

A separate dosing manual will detail the drug preparation and treatment administration to be followed for this study.

10.4.1.1 Drug Administration

Xisomab 3G3 will be supplied as sterile powder for injection via the IV route, upon reconstitution.

Matching placebo will be supplied as sterile powder for injection via IV route, upon reconstitution.

An unblinded pharmacist will be responsible for providing xisomab 3G3 or placebo to the blinded study personnel for administration as per the randomization scheme. All doses will be administered by a hand pushed IV infusion into a peripheral vein. The time of infusion for each dose level is outlined below:

Dose Level	Manual Push time
Cohort 1: 0.1 mg/kg	~1 minute
Cohort 2: 0.5 mg/kg	~2 minutes
Cohort 3: 2 mg/kg	~3 minutes
Cohort 4: 5 mg/kg	~5 minutes

Dosing will be done while subjects are supine in bed.

The subject weight recorded at check-in will be used to calculate the study drug dose.

The time at which the infusion is started and stopped must be recorded.

Should the need arise to change the infusion rate (i.e., due to an AE), changes to the infusion rate and the times at which those changes are made will be documented.

Hour 0 will correspond to the start of the infusion.

10.4.1.2 Planned Dose Levels

The planned dose levels are as follows:

Cohort 1: 0.1 mg/kg xisomab 3G3 or matching placebo

Cohort 2: 0.5 mg/kg xisomab 3G3 or matching placebo

Cohort 3: 2 mg/kg xisomab 3G3 or matching placebo

Cohort 4: 5 mg/kg xisomab 3G3 or matching placebo

Two sentinel subjects will be dosed (one placebo, one active) in Cohort 1 and data will be collected through Day 8 as described in the Study Events Flow Chart (Section 6). The next subject in the cohort will be dosed after evaluation of the sentinel subjects' Day 8 safety data. Each subject following these sentinel subjects will be dosed with an interval of 24-hour between subjects.

In Cohorts 2, 3, and 4, subjects will be dosed at an interval of 24 hours between subjects.

10.4.1.3 Additional Dose Levels

Additional subjects (N = 5 subjects per cohort; 4 active and 1 placebo) may be enrolled if it is deemed appropriate by the SRC to repeat a dose level or to study an interim dose level (lower than those planned) in a new cohort of subjects.

The IRB should be immediately notified of this revised approach.

10.4.1.4 Dose Escalation and Stopping Rules

A decision to proceed to the next higher dose administration will be made by SRC comprised of, but not limited to, the medical monitor, PI, and Sponsor Representative.

The SRC will review all pertinent blinded safety/tolerability data (e.g., physical examinations, ECGs, vital signs, clinical laboratory tests, and AEs) using all available data through Study Day 29 collected from all subjects dosed in the current cohort and from all subjects from previous cohorts to base dose escalation decision. At least 4 out of 5 subjects from the current cohort must complete scheduled safety procedures up to Day 29 prior to the decision to proceed to the next higher dosing cohort.

The safety data evaluation conducted by the SRC will be documented with the timing, recommendations, and decisions made by the SRC.

The maximum tolerated dose (MTD) will be considered as the last dose level before the dose level at which dose escalation is discontinued.

The SRC will make one of the following determinations:

1. To continue with the study as planned.

2. To continue with the study and add additional safety evaluations.

3. To stop the study or to continue with the study by adjusting to an intermediate dose between the current dose and the previous lower dose, if :

    a. At least 1 subject has a SAE or visit to the emergency room regardless of relatedness to the study drug, except SAEs that are clearly and incontrovertibly due to extraneous causes (see Section 11.1.9.4).

    b. At least 25% of subjects in a cohort experience a grade ≥ 2 AE.

Cohorts will be staggered to allow sufficient time for adequate review of safety and tolerability from the prior cohort.

PK data from a cohort may be used to guide the dose-escalation decision.

When applicable, a written statement fully documenting the reasons for study termination will be provided to the IRB.

10.4.2 Identity of Investigational Products

Investigational materials will be provided by the Sponsor as in Table 1.

Table 1: Product Descriptions

Product	Description
Test	Lyophilized xisomab 3G3 (~15 mg/mL) sterile powder for injection in formulation buffer [redacted].
Placebo	Lyophilized formulation buffer [redacted].

10.4.3 Method of Assigning Subjects to Treatment Groups

Each subject will be assigned a unique identification number upon screening. Subjects who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique randomization identification number prior to dosing, different from the screening number, and will receive the corresponding product according to a randomization scheme generated at Celerion.

Subjects will be randomized to receive either xisomab 3G3 or placebo, maintaining a 4:2 ratio in Cohort 1 and a 4:1 ratio in Cohorts 2, 3, and 4. Subjects in the first enrollment cohort will be numbered 1001 – 1006; subjects in the second enrollment cohort will be numbered 2001 – 2005, etc.

If replacement subjects are used, the replacement subject number will be 100 more than the original (e.g., Subject No. 1101 will replace Subject No. 1001).

10.4.4 Blinding

This is a double-blind, placebo-controlled study.

PI and clinical staff are blinded to the treatment; however safety review of clinical laboratories including aPTT will be done real-time. These results may have potential to show pharmacologic effect, but treatment will not be unblinded unless needed for safety reasons.

10.4.4.1 Maintenance of Randomization

A computerized randomization scheme will be created by a Celerion statistician and shall be considered blinded as per the following: the randomization is available only to the clinic pharmacy staff that is preparing the drug and is not involved in any other aspect of the study including administration of the drug. It will not be made available to the Sponsor, subjects, or members of the staff responsible for the monitoring and evaluation of safety assessments.

10.4.4.2 Procedures for Breaking the Blind Prior to Study Completion

One set of sealed envelopes containing the randomization code will be supplied to the PI or designee at the start of the study.

Breaking of the blind is expressly forbidden except in the event of a medical emergency where the identity of the drug must be known in order to properly treat the subject, or in the event of a safety interim analysis at the request of the sponsor (see Section 10.4.4.3).

In the event of a medical emergency, it is requested that the PI or designee make every effort to contact the Study Monitor or designee prior to breaking the blind. If breaking the blind is required because of a medical emergency, the treatment identity would be revealed by the PI or designee, for that subject only. In the event that the emergency is one, in which it appears that the other subjects may be at imminent risk, the blind may be broken for all subjects dosed at that dose level. The unblinding will be properly documented in the study file.

In all cases where the code is broken, the PI or designee should record the date and reason for code breaking.

At the end of the study, envelopes will be retained or destroyed according to site procedures unless specified otherwise by the Sponsor.

10.4.4.3 Interim Analysis

Safety:

All available blinded safety data will be reviewed by the SRC prior to dose escalation.

At the Sponsor's request, unblinded safety tables, figures, and data listings may be presented to the sponsor's medical expert and head of regulatory for the purposes of planning the next initial Phase 2 studies prior to database lock. These interim analyses will be performed on data that will be edit-checked and monitored.

A safety programmer and a biostatistician at Celerion who are not involved with the present study will be unblinded to prepare unblinded safety tables, figures, and data listings. All the personnel related to the present study will remain blinded.

Pharmacokinetics:

Preliminary PK analysis may be performed to evaluate the sampling time points as the study progresses and to guide the dose escalation decision. In such a case, interim PK analysis will not use the actual subject numbers in order to avoid breaking the blind.

Pharmacodynamics:

Preliminary PD analysis may be performed to evaluate the sampling time points as the study progresses and to guide the dose escalation decision. In such a case, interim PD analysis will not use the actual subject numbers in order to avoid breaking the blind.

10.4.4.4 Revealing of Randomization

In the absence of a medical emergency, the blinded randomization for this study will not be revealed until all data are entered in the database, edits checks are performed, queries closed, case report forms (CRFs) signed by the PI, and the database is officially locked.

10.4.5 Treatment Compliance

Drug administration will be performed by a qualified designee (e.g., nurse). Before and after IV infusion, the qualified designee will visually inspect the syringe to ensure that the subject has received the entire dose. In the case of an incomplete dosing (e.g., large droplet of study medication on the surface of the skin) as deemed by the PI and/or Sponsor, the subject may be withdrawn.

11. STUDY PROCEDURES

11.1 Safety Assessments

The Study Events Flow Chart (Section 6) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the PI or designee and/or the Sponsor for reasons related to subject safety.

For this study, the primary assessment is the safety and tolerability. Safety will be determined by evaluating physical examinations, vital signs, ECGs, clinical laboratory parameters, including but not limited to, hematology, serum chemistry profile, coagulation, urinalysis, injection site reaction, immunogenicity, and AEs as outlined in the Study Events Flow Chart (Section 6).

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

11.1.1 Body Height and Weight

Body height (centimeters) and body weight (kilograms) will be measured as outlined in the Study Events Flow Chart (Section 6). BMI will be calculated at screening.

11.1.2 Physical Examination

Full and abbreviated physical examinations will be performed as per Study Events Flow Chart (Section 6).

Full physical examinations will include, at a minimum, assessment of the following systems: skin, head, ears, eyes, nose and throat, respiratory system, cardiovascular system, gastrointestinal system, neurological condition, blood and lymphatic systems, and the musculoskeletal system.

Abbreviated physical examinations will include at the minimum, examination of respiratory, cardiovascular, and gastrointestinal systems, with the option for further examination of additional systems as necessary based on reported symptoms/AEs.

Symptom-driven physical examination may be performed at other times, if deemed necessary by the PI or designee.

Medical history will be recorded at screening.

11.1.3 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure, and heart rate will be measured as outlined in the Study Events Flow Chart (Section 6). Additional vital signs may be taken at any other times, if deemed necessary by the PI or designee.

Vital sign measurements will be performed with subjects in a seated position, except when they are supine or semi-reclined because of study procedures and/or AEs (e.g., nausea,

dizziness) or if deemed necessary by the PI or designee.

Vital signs will be measured within 24 hours prior to dosing for the predose time point. When scheduled postdose, vital signs will be performed within approximately 10 minutes of the scheduled time point.

11.1.4 Electrocardiogram Monitoring

Single 12-lead ECGs will be performed as outlined in the Study Events Flow Chart (Section 6). Additional ECGs may be taken at any other times, if deemed necessary by the PI or designee.

ECGs will be performed with subjects in a supine position. All ECG tracings will be reviewed by the PI or designee.

ECGs will be measured within 24 hours prior to dosing for the predose time point. When scheduled postdose, ECGs will be performed within approximately 20 minutes of the scheduled time point.

11.1.5 Clinical Laboratory Tests

All tests listed below will be performed as per Study Events Flow Chart (Section 6). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the PI or designee.

Hematology
- Hemoglobin
- Hematocrit
- Total and differential leukocyte count
- Red blood cell count
- Platelet count

Coagulation
- PT/INR
- aPTT

Urinalysis
- pH
- Specific gravity
- Protein***
- Glucose
- Ketones
- Bilirubin
- Blood***
- Nitrite***
- Urobilinogen
- Leukocyte esterase***

Serum Chemistry*
- BUN
- Bilirubin (total and direct)
- ALP
- AST
- ALT
- LDH
- Albumin
- Sodium
- Potassium
- Chloride
- Glucose (fasting)
- Creatinine**

Additional Tests
- HIV test
- HBsAg
- HCV
- Urine drug screen
  - Opiate
  - Amphetamines
  - Cocaine
  - Cannabinoids
- Urine alcohol screen
- Bleeding time
- Serum pregnancy test (for females only)
- FSH (for postmenopausal females only)

* Serum chemistry tests will be performed after at least an 8-hour fast (except for the 8-hour time point); however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours before the serum chemistry sample is taken.

** At screening, creatinine clearance will be calculated using the Cockcroft-Gault formula.

*** If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.

11.1.6 Check-In Questionnaire

A check-in questionnaire will be reviewed for each subject to ensure that they remain eligible for the study. The questions will be based on the inclusion and exclusion criteria and study restrictions.

11.1.7 Injection Site Reaction Assessment

The monitoring of AEs will pay special attention to potential injection site reactions. Therefore, inspection of the injection site and surrounding area will be performed. Any abnormal findings will be reported as AEs. Injection site reactions will be evaluated as outlined in the Study Events Flow Chart (Section 6). Prior to dosing, the injection site will be examined. When scheduled postdose, injection site examinations will be performed within approximately 20 minutes of the scheduled time point. Reactions will be rated according to the FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials [3] as follows:

Local Reaction	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
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
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest
Erythema/Redness*	2.5 – 5 cm	5.1 – 10 cm	> 10 cm
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

* 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.

11.1.8 Immunogenicity Assessment

Blood samples for immunogenicity assessment will be performed from the PK blood collection tubes as per Study Events Flow Chart (Section 6).

Instruction for blood sampling, collection, and processing will be provided separately.

11.1.9 Adverse Events

11.1.9.1 Adverse Event Definition

An AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. [4]

Prolonged aPTT is an expected pharmacological effect of xisomab 3G3 and will, therefore, not be considered an AE.

11.1.9.2 Monitoring

Subjects will be monitored throughout confinement for adverse reactions to the study drug and/or procedures. Subjects will be asked how they are feeling once per day during confinement and at each return/follow-up visit.

AEs (whether serious or non-serious) and clinically significant abnormal laboratory test value(s) will be evaluated by the PI or designee and treated and/or followed up until the symptoms or value(s) return to normal, or acceptable levels, as judged by the PI or designee.

Treatment of SAEs will be performed by a licensed medical provider, either at Celerion or at a nearby hospital emergency room. Where appropriate, medical test(s) and/or examination(s) will be performed to document resolution of event(s). Outcome may be classified as resolved, improved, unchanged, worse, fatal, or unknown (lost to follow up).

11.1.9.3 Reporting

All AEs that occurred during this clinical trial will be recorded. AEs will be coded using the most current MedDRA® available at Celerion.

The PI or designee will review each event and assess its relationship to drug treatment (likely, probably, possibly, unlikely or unrelated). Each sign or symptom reported will be graded on the FDA (Center for Biologics Evaluation and Research) toxicity grading scale for healthy volunteers 4-point severity scale (Grade 1, 2, 3 and 4).[3] The date and time of onset, time relationship to drug dosing, duration, and outcome of each event will be noted.

Relationship of AE:

The relationship of each AE to the study drug will be assessed using the following definitions:

Unrelated	▪ The adverse event must clearly be caused by the participants clinical state, or the study procedure/conditions ▪ Definitely not related to drug ▪ Temporal sequence of an adverse event onset relative to administration of drug not reasonable ▪ Another obvious cause of an adverse event
Unlikely	▪ Time sequence is unreasonable ▪ There is another more likely cause for an adverse event
Possibly	▪ Corresponds to what is known about the drug ▪ Time sequence is reasonable ▪ Could have been due to another equally, likely cause
Probably	▪ Is a known effect of the drug ▪ Time sequence from taking drug is reasonable ▪ Ceases on stopping the drug ▪ Cannot be reasonably explained by the known characteristics of the participants clinical state
Likely	▪ Is a known effect of the drug (e.g. listed in IB) ▪ Time sequence from taking drug is reasonable ▪ Event stops upon stopping drug, event returns upon restarting drug Note: Prolonged aPTT is an expected pharmacological effect of xisomab 3G3 and will, therefore, not be considered an AE.

Severity of AE:

Severity rating used during the study will be based on the the toxicity grading scale tables present in the FDA (Center for Biologics Evaluation and Research) toxicity grading scale for healthy volunteers 4-point severity scale (Grade 1, 2, 3 and 4).[3]

The following definitions for rating severity will be used for AEs not identified in the guidance:

Mild (Grade 1)	The AE does not interfere with daily activity
Moderate (Grade 2)	The AE interferes with daily activity, but no medical intervention is required

Severe (Grade 3)	The AE prevents daily activity and requires medical intervention
Potentially Life-threatening (Grade 4)	Emergency room visit or hospitalization is required

11.1.9.4 Serious Adverse Events

If any AEs are serious, as defined by the FDA Code of Federal Regulations (CFR), Chapter 21, special procedures will be followed. All SAEs will be reported to the Sponsor via fax or e-mail within one working day of becoming aware of the event, whether or not the serious events are deemed drug-related. All serious event reporting will adhere to 21 CFR 312.32 for Investigational New Drugs (IND) and to the Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE, dated December 2012. [4] The IRB will be notified of the Alert Reports as per FDA regulations.

A SAE is any AE or suspected adverse reaction that in the view of either the PI (or designee) or Sponsor, results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or 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 patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above 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.

Life-threatening is defined as an AE or suspected adverse reaction that in the view of the PI (or designee) or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Unexpected is defined as an AE or suspected adverse reaction that is not listed in the IB or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

If a SAE occurs to a subject on this study, contact the Sponsor personnel listed in Section 3.

11.2 Pharmacokinetic Assessments

11.2.1 Blood Sampling and Processing

For all subjects, blood samples for the determination of free xisomab 3G3 will be collected in sodium citrate blood collection tubes at scheduled time points as delineated in the Study Events Flow Chart (Section 6).

The sample times for PK collection are in relation to the start of infusion.

Instruction for blood sampling, collection, and processing will be provided separately.

Following completion of the samples analysis, leftover plasma samples will be shipped to the Sponsor, as per their instructions provided seperately. Additional analysis for exploratory purposes, including but not limited to actor XIa activity, will be performed on leftover plasma samples at the Sponsor's discretion.

11.2.2 Analytical Method

Plasma sample analysis will be performed using validated bioanalytical methods.

11.3 Pharmacodynamic Assessments

For all subjects, blood samples for the determination of aPTT will be collected in blood collection tubes containing sodium citrate (3.2%) at scheduled time points as delineated in the Study Events Flow Chart (Section 6).

11.4 Blood Volume for Study Assessments

Table 2: Blood Volume during the Study

Sample Type	Number of Time Points	Approximate Volume per Time Point * (mL)	Approximate Sample Volume Over Course of Study (mL)
Screening laboratory safety tests (including hematology, serum chemistry, serology, and coagulation), FSH (for postmenopausal female subjects only) and serum pregnancy (for female subjects only).	1	16	16
On-study hematology	at least6†	4	24 or more
On-study serum chemistry (this includes serum pregnancy for female subjects only when scheduled at the same time)	at least 6†	8.5	51 or more
On-study coagulation (PT/INR only)	at least 5†	**	**
On-study coagulation (PT/INR and safety aPTT)	2	3.5	7
Blood for PK (free xisomab 3G3)†	at least 15†	10	150 or more
Blood for PD (aPTT)†	at least 15†	3.5	52.5 or more
Blood for Immunogenicity	at least 3	††	††
		Total Blood Volume (mL)→	300.5 or more †,†††

* Represents the largest collection tube that may be used for this (a smaller tube may be used).

** PT/INR samples will be taken from aPTT samples, either the safety coagulation sample or the PD samples. Additional PT/INR will be taken at least 2 days after discharge to confirm the PT/INR discharge value of ≤ 3.5; If this sample does not correspond with a safety coagulation sample or the PD samples (aPTT), an extra 3.5 mL of blood will be collected.

† PK and PD samples will be collected for a minimum of 28 days postdose (Day 29). If by Day 29 aPTT values have not returned within ± 10% of the baseline value or the normal range, sampling will continue every 7 days (± 2 days) for PK, PD, and, as per PI discretion, safety clinical laboratories test until the ± 10% of baseline value or to the normal range is reached or a maximum of ~500 mL of blood is collected from the subject. Subjects who terminate the study early will also be asked to return every 7 days (± 2 days) for aPTT monitoring until aPTT values return within ± 10% of baseline value or the normal range.

†† Sample for immunogenicity will be taken from the PK sample tube. If this sample does not correspond with a PK sample, an extra 10 mL of blood sample will be collected.

††† If additional safety, PK, or PD analysis is necessary or if larger collection tubes are required to obtain sufficient plasma/serum for analysis, additional blood may be obtained (up to a maximum of ~500 mL; this volume could be exceeded only with agreement of the PI on a case-by-case basis).

12. DATA ANALYSIS

Data will be handled and processed according to Celerion Standard Operating Procedures (SOPs), which are written based on the principles of GCP.

12.1 Statistical Analysis

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a Statistical Analysis Plan (SAP). The SAP will be prepared by Celerion and agreed upon with the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate and included in the SAP.

12.1.1 Sample Size Calculation

The sample size chosen for this study was selected without statistical considerations. It has been determined adequate to meet the study objectives. Cohorts of up to 6 (4:2 ratio of active study drug:placebo) and 5 subjects (4:1 ratio of active study drug:placebo) are sufficient to characterize the single-dose safety, tolerability, PK, and PD profile.

12.1.2 Subjects to Analyze

Safety population: All subjects who received the study drug (active or placebo) will be included in the safety summary.

PK population: All subjects receiving the active drug and having any measurable plasma concentration of study drug will be included in the PK data set. All subjects who comply sufficiently with the protocol and display an evaluable PK profile (e.g., exposure to treatment, availability of measurements and absence of major protocol violations) will be included in the statistical analyses.

PD population: All subjects receiving the study drug (active or placebo) and having any measurable PD data will be included in the PD data set.

12.1.3 Safety Analysis

The following analyses will be performed; however no formal inferential statistics will be done on safety assessments.

The placebo subjects from all cohorts will be pooled into a single placebo group for all summaries and presentations.

Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data.

Adverse Events:

AEs will be coded using the most current version of MedDRA® available at Celerion.

A by-subject AE data listing, including verbatim term, preferred term, treatment, severity, and relationship to drug, will be provided.

The number of subjects experiencing TEAEs and number of TEAEs will be summarized by treatment using frequency counts.

Injection site reaction will be assessed.

Medical History and Physical Examination:

Medical history will be listed by subject.

Changes in physical examinations will be described in the text of the final report.

Clinical Laboratory Results, Electrocardiograms, and Vital Signs Measurements:

All clinical laboratory results, 12-lead ECGs, vital signs measurements, and their change from baseline, will be summarized by treatment and time point of collection.

A shift table describing out-of-normal range shifts will be provided for clinical laboratory results.

Concomitant Medications:

Concomitant medications will be listed by treatment.

Immunogenicity:

ADA detection will be reported and summarized descriptively.

12.1.4 Pharmacokinetic Analysis

12.1.4.1 Pharmacokinetic Parameters

The following PK parameters will be computed, as appropriate, for plasma free xisomab 3G3 from the individual plasma concentrations using a noncompartmental approach.

AUC_{0-t}:	The area under the plasma concentration-time curve, from time 0 to the last measurable non-zero concentration, as calculated by the linear trapezoidal method.
AUC_{0-inf}:	The area under the plasma concentration-time curve from time 0 extrapolated to infinity. AUC_{0-inf} is calculated as the sum of AUC_{0-t} plus the ratio of the last measurable plasma concentration to the elimination rate constant.

$AUC_{\%extrap}$:	Percent of $AUC_{0\text{-}inf}$ extrapolated, represented as $(1 - AUC_{0\text{-}t}/AUC_{0\text{-}inf})*100$.
$AUMC_{0\text{-}inf}$:*	Area under the moment curve from time 0 to the last measurable concentration, = $AUMC_{0\text{-}t} + [(tlast \times Ct)/ K_{el}] + Ct/(K_{el})^2$
C_{max}:	Maximum observed concentration.
T_{max}:	Time to reach C_{max}. If the maximum value occurs at more than one time point, T_{max} is defined as the first time point with this value.
K_{el}:	Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve. The parameter will be calculated by linear least-squares regression analysis using the maximum number of points in the terminal log-linear phase (e.g., three or more non-zero plasma concentrations).
$T_{½}$:	Apparent first-order terminal elimination half-life will be calculated as $0.693/ K_{el}$.
CL:	Apparent total plasma clearance calculated as $[Dose/AUC_{0\text{-}inf}]$.
MRT:*	Mean residence time = $AUMC_{0\text{-}inf}/AUC_{0\text{-}inf}$ (for IV infusion)
V_{ss}:	Total apparent volume of distribution following single IV dose administration calculated as V_{ss} = MRT x CL.

* $AUMC_{0\text{-}inf}$ and MRT values will be used for V_{ss} calculation but will not be listed in the PK tables.

Additional PK parameters may be computed if deemed appropriate.

No PK parameters will be calculated for subjects with 2 or fewer consecutive time points with detectable concentrations.

No value for K_{el}, $T_{½}$, $AUC_{0\text{-}inf}$, $AUC_{\%extrap}$, CL, and V_{ss}, as appropriate, will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

Individual and mean plasma concentration time curves (both linear and log-linear) will be included in the final report.

12.1.5 Statistical Methods for Pharmacokinetic Analyses

Values will be calculated for the plasma concentrations and the PK parameters listed in Section 12.1.4.1 using appropriate summary statistics to be fully outlined in the SAP.

Figures will be created to display mean and individual free xisomab 3G3 concentration-time curves.

Additional analyses may be performed as deemed necessary upon review of the data.

12.1.6 Pharmacodynamic Assessments

aPTT values will be listed and presented graphically.

PD parameters may be calculated if deemed appropriate.

12.1.7 Assessment of Efficacy

Efficacy will not be assessed in this study.

13. STUDY ADMINISTRATION

13.1 Ethics

13.1.1 Institutional Review Board

This protocol will be reviewed by the Chesapeake Research Review, Inc. IRB, and the study will not start until the IRB has approved the protocol or a modification thereof. The IRB is constituted and operates in accordance with the principles and requirements described in the US Code of Federal Regulations (21 CFR Part 56). The IRB is compliant to International Conference on Harmonisation (ICH) guidelines, and may be reached at:

Chesapeake IRB
6940 Columbia Gateway Drive, Suite 110
Columbia, Maryland 21046, USA
Tel.: +1 410 884-2900

13.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, 21 CFR Parts 50, 56, and 312, the ethical principles set forth in the Declaration of Helsinki, GCP, and the ICH harmonized tripartite guideline regarding GCP (E6 Consolidated Guidance, April 1996).

13.1.3 Subject Information and Consent

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the subjects in non-technical terms. Subjects will be required to read, sign and date an ICF summarizing the discussion at screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Subjects will be given a copy of their signed ICF.

13.2 Termination of the Study

The Sponsor reserves the right to discontinue the study and Celerion reserves the right to terminate the study in the interest of subject welfare, at any time.

13.3 Data Quality Assurance

Standard operating procedures are available for all activities performed at Celerion relevant to the quality of this study. Designated personnel of Celerion will be responsible for implementing and maintaining quality assurance (QA) and quality control systems to ensure that the trial is conducted, and that data are generated, documented and reported in compliance with the study protocol, GCP and GLP requirements as well as applicable regulatory requirements and local laws, rules and regulations relating to the conduct of the clinical study.

The Clinical Study Report will be audited by the QA department and the QA audit certificate will be included in the study report.

All clinical data will undergo a 100% quality control check prior to clinical database lock. Edit checks are then performed for appropriate databases as a validation routine using SAS® to check for missing data, data inconsistencies, data ranges etc. Corrections are made prior to statistical database lock.

13.4 Direct Access to Source Data/Documents

The PI must maintain, at all times, the primary records (i.e., source documents) of each subject's data. Examples of source documents are laboratory reports, drug inventory, study drug label records, and CRFs that are used as the source.

Celerion will ensure that the sponsor, IRB and inspection by domestic and foreign regulatory authorities will have direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring, auditing (ICH[E6] 5.1.2 & 6.10) and inspection. In the event that other trial-related monitoring should be done by other parties, they will be required to sign a confidentiality agreement prior to any monitoring and auditing.

13.5 Study Supplies

The Sponsor will supply sufficient quantities study drug and matching placebo to allow completion of this study. The lot numbers, manufacture dates, and expiration dates (if available) of the drugs supplied will be recorded in the final report.

The investigational product(s) will be shipped to a designee at the study site and must be stored in a pharmacy or locked and secured in a storage facility with controlled temperature. Humidity in the room will be monitored. The room is accessible only to those individuals authorized by the PI.

Records will be made of the receipt and dispensing of the study drugs supplied. At the conclusion of the study, any unused study drugs (including placebo) as well as original containers (even if empty), will be retained by Celerion, returned to the Sponsor or designee, or destroyed, as per Sponsor instructions. If no supplies remain, this fact will be documented in the pharmacy product accountability records.

13.6 Data Handling and Record Keeping

Celerion standard CRFs will be used. CRFs are printed directly from the ClinQuick® database. Each CRF is reviewed and signed off by the PI.

ClinQuick® is a fully integrated, study management and data capture system designed and built by Celerion for use in Phase 1 clinical research centers. ClinQuick® will be used for all data that can be captured electronically via barcode or electronic acquisition (e.g., vital signs, meal times, blood draw times, etc.). Electronic changes will be traceable through computer capture.

Other data (e.g., medical history, inclusion/exclusion criteria, etc.) will be entered into ClinQuick® by remote data entry or via double data entry by 2 different associates using an automated verification system within ClinQuick®. AEs and concomitant medications will be

entered into ClinQuick® by single data entry.

Visual and computerized methods of data validation will be applied in order to ensure accurate, consistent, and reliable data for the subsequent statistical analysis.

These procedures aim to detect out-of-range values, contradictory data, abnormal evolutions over time, and possible undetected protocol violations (eligibility criteria, time and medication compliance, etc.).

All raw data generated in connection with this study, together with the original copy of the final report, will be retained by Celerion until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the PI/Institution as to when these documents no longer need to be retained.

13.7 Report Format

According to the ICH Harmonized Tripartite Guideline (Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use M4 and the ICH M2 Expert Working Group), the final report will be written according to the ICH E3 Guideline (Structure and Content of Clinical Study Reports).

13.8 Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be discussed between Sponsor and the PI or designee. All revisions and/or amendments to the protocol in writing must be approved by the Sponsor, the PI or designee, and the IRB before implementation.

13.9 Publication Policy

All unpublished information given to Celerion by the Sponsor shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

The data generated by this study are considered confidential information and the property of the Sponsor. This confidential information may be published only in collaboration with participating personnel from the Sponsor or upon Sponsor’s written consent to publish the article.

14. REFERENCES

1. Xisomab 3G3. Aronora, Inc. Investigator Brochure. Version Number 1; 01 Jan 2017.

2. FDA Guidance for Industry: Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. July 2005. Available online: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078932.pdf

3. FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. September 2007. Available online: http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf

4. FDA Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE, dated December 2012. Available online at: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM227351.pdf

Appendix 1 Clinical Laboratory Reference Ranges

Name of Laboratory:	Celerion	
Adress:	2420 West Baseline Road Tempe, Arizona 85283, USA	
Laboratory Test	Adult Reference Range*	(Male and Female)
Hematology		
Platelet Count	162-399 Thou/µL	Both
Coagulation		
PT/INR	0.9-1.1	Both
aPTT	23-32 seconds	Both
Bleeding Time**	2.0-8.0 minutes	Both
Serum Chemistry		
ALP	47-132 U/L	Male
	41-129 U/L	Female
ALT	10-60 U/L	Both
AST	14-47 U/L	Both
LDH	125-248 U/L	Both
BUN	7.0-21.0 mg/dL	Male
	6.0-20.0 mg/dL	Female
Creatinine	0.67-1.22 mg/dL	Male
	0.44-0.93 mg/dL	Female

* Based on Celerion Screening Population
** Using Simplate method