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Clinical Protocol

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy/Potency of a Single Dose of Xisomab 3G3, Administered at the Beginning of a Regular Hemodialysis Procedure, in Patients with End-Stage Renal Disease on Chronic Hemodialysis

Celerion Project No.: CA23900

Sponsor Project No.: 3G3-18-02

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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
14June2018 by Natacha Benrimoh	Final Protocol, Amendment 1 Following review by the Institutional Review Board, this protocol is being amended to provide justification for the use of a placebo-control design. In addition, information on safety measures that will be undertaken by the Investigators should there be clotting in the extracorporeal circuit has been added. Thus, Section 8.4.1 Rationale for this Study and Study Design, Section 8.5 Risks and/or Benefits to Patients, and Section 11.3 Early Termination of Patients from the Study were updated. Section 13.3 Hemodialysis Procedure and Blood Clots in the Dialyzer Cartridge was created. In addition, the following changes were made: - Section 11.2 Exclusion criteria, criterion 2 was updated (changes in strikethrough and additions in bold): "**With the exception of unfractionated heparin during HD,** ~~C~~**c**oncomitant or prior use of anticoagulant/antiplatelet agents (e.g., **low molecular weight heparins,** warfarin, apixaban, bivalirudin, ticagrelor, edoxaban, dabigatran, rivaroxaban, clopidogrel, prasugrel, ticlopidine, eptifibatide, tirofiban, dipyridamole, **diclofenac**, and all **other** NSAIDs) that may affect hemostasis for 2 weeks prior to check-in on Day -8 and throughout the study." - Section 11.2 Exclusion criteria, criterion 3 was updated (changes in strikethrough and additions in bold): "Use of u**nfractionated** heparin **for HD sessions** from check-in on Day -8 and throughout the study." - Section 11.2 Exclusion criteria, criterion 9: The value for hemoglobin concentration at screening was increased from 8.5 g/dL to 10 g/dL. The hemoglobin limit was increased to allow for the possibility of blood loss of up to 228 mL if there is a clot in the dialyzer circuit. Also, the 5 other clinical laboratory values had no specific timing on when these values were required; thus, "at screening" was added for these clinical laboratory tests. - Section 13.6 Dialysate Analysis; this section was added as samples of the dialysate will be taken for future analysis (e.g., assessment of urea or drug level in the dialysate). Samples will be stored for up to 5 years).

	- Section 13.7.1 Blood Sampling and Processing, wording was added that leftover samples would be stored for up to 5 years. Updates in blood volume (i.e., correction in number of samples were made increasing the total blood volume by about 5 mL (from 430 mL to 435.9 mL) Minor editorial, consistency, and formatting updates were made throughout the protocol.
25May2018 by Natacha Benrimoh	Final Protocol

2 PRINCIPAL INVESTIGATOR AND SPONSOR – SIGNATORIES

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy/Potency of a Single Dose of Xisomab 3G3, Administered at the Beginning of a Regular Hemodialysis Procedure, in Patients with End-Stage Renal Disease on Chronic Hemodialysis

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5 SYNOPSIS

Compound:	xisomab 3G3 (anti-factor [F] XI monoclonal antibody, IgG4)
	Active ingredient: xisomab 3G3 (~15 mg/mL) Excipients: 8% sucrose, 10 mM histidine, 30 mM arginine HCl, 10 mM methionine, 80 ppm polysorbate 80
Clinical Indication:	Prevention or treatment of thrombotic and thromboembolic diseases
Study Phase:	Phase 2
Study Objectives:	The primary objective of this study is: • To assess the safety and tolerability of a single dose of xisomab 3G3 when injected through a port into the proximal (arterial) dialysis line immediately after initiation of a hemodialysis (HD) procedure in patients with end stage renal disease (ESRD). The secondary objectives of this study are: • To assess the pharmacodynamics (PD) of a single dose of xisomab 3G3 when injected through a port into the proximal (arterial) dialysis line immediately after initiation of a HD procedure in patients with ESRD. • To assess the efficacy of a single dose of xisomab 3G3 on HD efficiency when injected through a port into the proximal (arterial) dialysis line immediately after initiation of a HD procedure in patients with ESRD. • To assess the pharmacokinetics (PK) of a single dose of xisomab 3G3 when injected through a port into the proximal (arterial) dialysis line immediately after initiation of a HD procedure in patients with ESRD.
Summary of Study Design:	This is a phase 2, randomized, double-blind, placebo-controlled, single-dose study of xisomab 3G3 designed to evaluate the safety, efficacy/potency, and PK at 2 dose levels administered to patients with ESRD undergoing HD. Patients will be enrolled into Cohort 1 or Cohort 2; cohorts will be dosed sequentially. Within a cohort, patients will be randomized to active drug or placebo as summarized below:

	<table><tr><th>Cohort</th><th>Treatment</th><th>Active:Placebo</th><th>Cohort Size</th></tr><tr><td>1</td><td>Infusion dose of 0.25 mg/kg xisomab 3G3 or placebo</td><td>2:1</td><td>9-12</td></tr><tr><td>2</td><td>Infusion dose of 0.5 mg/kg xisomab 3G3 or placebo</td><td>2:1</td><td>9-12</td></tr></table> This study includes a screening period of 28 days prior to checking-in to the clinical research unit on Day -8. From Day -7 (one week prior to dosing on Day 1) through Day -1, all patients will undergo HD 3 times and will be assessed for all scheduled procedures and endpoints before and after each HD session as per the Study Events Flow Chart (Section 6). On Study Day 1, prior to dosing, patients will undergo baseline measurements followed by initiation of a regular HD procedure, consistently using only one type of dialyzer cartridge in each patients. Immediately after the start of blood perfusion, a single dose of xisomab 3G3 or matching placebo will be injected through a port into the flowing arterial blood in the proximal dialysis line. Patients will continue to undergo HD procedures and scheduled assessments from Day 1 through Day 12. Study assessments will include physical examinations, vital signs, electrocardiogram (ECGs), clinical laboratory tests, HD vascular access site (AV fistula or AV graft) reaction, antibody titer (immunogenicity), adverse events (AEs), PD blood sampling (coagulation parameters), and PK blood sampling to be performed throughout the study according to the Study Events Flow Chart (Section 6). On Days -7, -5, and -3 and Days 1, 3, 5, and 12, bleeding time from the HD vascular access sites on the AV fistula or AV graft (ladder or buttonhole technique) will be evaluated at the end of the HD session. The dialyzer cartridge will be rinsed and visually inspected at the end of the HD procedure and graded against a standardized visual assessment scale. After visual assessment, the used and rinsed dialyzer cartridge will be frozen and saved for later retained content (deposited blood-derived material) analysis. The number of dialyzer cartridges used for the HD session will be recorded. All patients who received the study drug or placebo (including patients who terminate the study early) will undergo follow-up procedures at the Clinical Research Unit (CRU) approximately 12 days after dosing.
Number of Patients:	A total of up to 24 adult male and female patients will be enrolled; 9-12 patients are planned for each cohort. In each cohort, an attempt will be made to enroll at least 50% of females and at least 30% of a race/ethnicity minority group. An

	attempt will also be made to approximately match key characteristics, including sex, average age, and weight per cohort.
Dosage, Dosage Form, Route, and Dose Regimen:	On Day 1, patients in each cohort will receive a single dose of xisomab 3G3 or placebo injection into the proximal (arterial) dialysis line on one occasion. Cohort 1 will be conducted prior to initiation of Cohort 2. Planned doses will be as follows: Cohort 1: 0.25 mg/kg xisomab 3G3 or matching placebo Cohort 2: 0.5 mg/kg xisomab 3G3 or matching placebo
Key Assessments:	**Safety** Safety assessment will include physical examinations, vital signs, ECGs, clinical laboratory tests, vascular access site reaction, bleeding time, and AEs. Number/severity of AE will be tabulated and summary statistics for the 12-lead ECGs, vital signs, and clinical laboratory tests may be computed and provided, as deemed clinically appropriate. **Pharmacodynamics:** Efficacy/potency assessment will be measured as efficiency of the hemodialysis by assessing thrombus accumulation (ranked by visual inspection) in the dialyzer cartridge, protein accumulation in the HD filter, BUN and potassium blood levels, length of HD, measurement of urea removed by 3 hours of dialysis, and total dialysate urea (Kt/V and urea reduction ratio [URR)]. Coagulation tests will also be performed. Change from baseline will be summarized by treatment (2 active dose levels and pooled placebo) and per timepoints using descriptive statistics. **Pharmacokinetics:** The following PK parameters will be calculated for xisomab 3G3 in plasma, as appropriate: AUC0-t, AUC0-inf, AUC%extrap, Cmax, Tmax, Kel, t½, CL, and Vss. PK parameters will be summarized by dose level using descriptive statistics. **Immunogenicity:** Development of antibodies against the study drug will be evaluated by determining the anti-drug antibody (ADA) titer.

6 STUDY EVENTS FLOW CHART

Study Procedures [a:]	**Screening** [b:] (Day -37 to Day -9)	**Study Days**								
		Evaluation Period								
Days →		**-8**	**-7**		**-6**	**-5**		**-4**	**-3**	
HD →			**HD** [d:]			**HD** [d:]			**HD** [d:]	
Hours →		**C-I** [c:]	**start**	**end**		**start**	**end**		**start**	**end**
Administrative Procedures										
Informed Consent	X									
Inclusion/Exclusion Criteria	X	X								
Medical History	X									
Safety Evaluations										
Full Physical Examination [e:]	X	X								
Height	X									
Weight	X	X	X [f:]	X [g:]	X	X [f:]	X [g:]	X	X [f:]	X [g:]
12-Lead Safety ECG	X	X								
Vital Signs (HR, BP, RR, and T)	X	X	X [f:]			X [f:]			X [f:]	
Bleeding of Access Site				X [g:]			X [g:]			X [g:]
Hem, Serum Chem [h:], and UA [i:]	X	X								
Coagulation [j:]	X		X [f:]	X [g:]		X [f:]	X [g:]		X [f:]	X [g:]
Platelet Count [s:]			X [f:]	X [g:]		X [f:]	X [g:]		X [f:]	X [g:]
Serum Pregnancy Test (♀only)	X	X								
Serum FSH (PMP ♀only)	X									
Urine/Saliva Drug and Alcohol Screen	X	X								
HIV/Hepatitis Screen	X									
AE Monitoring		X								
ConMeds Monitoring	X	X								
Other Procedures										
Blood BUN and Potassium (for Kt/V and URR) [s:]			X [f:]	X [g:]		X [f:]	X [g:]		X [f:]	X [g:]
Dialysate Analysis			X [k:]	X [k:]		X [k:]	X [k:]			
Visual Assessment and Processing of Dialyzer Membrane				X [l:]			X [l:]			X [l:]
Confinement in the CRU		X								
Visit	X									

Study Procedures [a:]	**Study Days**																			
	PK/PD Period																			
Days →	**1**											**2**	**3**			**4**	**5**			**6**
HD →	**HD** [d:]													**HD** [d:]				**HD** [d:]		
Hours →	**0-0.016**	**0.167**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**12**	**16**	**24**	**48**	**start**	**end**	**72**	**96**	**start**	**end**	**120**
Safety Evaluations																				
Abbreviated Physical Examination [e:]	X [m:]																			X [p:]
Weight	X [f:]					X [g:]						X		X [f:]	X [g:]	X		X [f:]	X [g:]	X [p:]
12-Lead Safety ECG	X [m:]																			X [p:]
Vital Signs (HR, BP, RR and T)	X [m:]			X										X [f:]				X [f:]		X [p:]
Bleeding of Access Site						X [g:]									X [g:]				X [g:]	
Hem, Serum Chem [h:], and UA [i:]	X [m:]																			X [p:]
Coagulation [j:]	X [f:]					X [g:]								X [f:]	X [g:]			X [f:]	X [g:]	X [p:]
Platelet Count [s:]	X [f:]					X [g:]								X [f:]	X [g:]			X [f:]	X [g:]	
AE Monitoring	X																			
ConMeds Monitoring	X																			
Study Drug Administration / PK/PD/Immunogenicity																				
Xisomab 3G3 Administration [n:]	X																			
Blood for free xisomab 3G3 PK	X [o:]	X	X	X	X	X	X	X	X	X	X	X	X [o:]				X [o:]			X [p:]
Blood for free xisomab 3G3 PD (aPTT) [s:]	X [o:]	X	X	X	X	X	X	X	X	X	X	X	X [o:]				X [o:]			X [p:]
Blood for Immunogenicity	X [m:]																			
Blood BUN and Potassium (for Kt/V and URR) [s:]	X [f:]					X [g:]								X [f:]	X [g:]			X [f:]	X [g:]	
Dialysate Analysis			X [k:]			X [k:]								X [k:]	X [k:]					
Visual Assessment and Processing of Dialyzer Membrane						X [l:]									X [l:]				X [l:]	
Other Procedures																				
Vascular Access Site Reaction	X [m:]					X [q:]									X [q:]				X [q:]	
Confinement in the CRU	X																			
Return Visit																				

Study Procedures [a:]	**Study Days**									
	Follow-up Period									
Days →	**7**	**8**		**9**	**10**		**11**	**12**		
HD →		**HD** [d:]			**HD** [d:]			**HD** [d:]		
Hours →		**start**	**end**		**start**	**end**		**start**	**end**	
Safety Evaluations										
Abbreviated Physical Examination [e:]										X [r:]
Weight		X [f:]	X [g:]		X [f:]	X [g:]		X [f:]	X [g:]	
12-Lead Safety ECG										X [r:]
Vital Signs (HR, BP, RR, and T)		X [f:]			X [f:]			X [f:]		X [r:]
Bleeding of Access Site									X [g:]	
Hem, Serum Chem [h:], and UA [i:]										X [r:]
Coagulation [j:]								X [f:]	X [g:]	X [r:]
Platelet Count [s:]								X [f:]	X [g:]	
Serum Pregnancy Test (♀only)										X [r:]
AE Monitoring	X									X
ConMeds Monitoring	X									
Study Drug Administration / PK/PD/Immunogenicity										
Blood for free xisomab 3G3 PK										X [r:]
Blood for free xisomab 3G3 PD (aPTT) [s:]		X [o:]			X [o:]					
Blood for Immunogenicity										X [r:]
Other Procedures										
Blood BUN and Potassium (for Kt/V and URR)								X [f:]	X [g:]	
Dialysate Analysis								X [k:]	X [k:]	
Visual Assessment and Processing of Dialyzer Membrane									X [l:]	
Return Visits		X			X			X		

a: For details on Procedures, refer to Section 13

b: Within 28 days prior to Day -8.

c: Patients will be admitted to the CRU on Day -8, at the time indicated by the CRU and will remain confined up to Day 6 or prior early termination.

d: Patients will undergo hemodialysis 3 times a week, on Day -7, Day -5, Day -3, and Day 1, Day 3, Day 5, Day 8, Day 10, and Day 12. For each patient, the hemodialysis will last at least 3 hours as per patient standard schedule which will be the same throughout the study.

e: Symptom-driven physical examination may be performed at other times, at the PI's or designee's discretion.

f: To be performed ~ 1 hour prior to the start of hemodialysis.

g: To be performed at the end of hemodialysis.

h: Samples for serum chemistry will be obtained following a fast of at least 4 hours, however, in case of dropouts or rechecks, patients may not have fasted for 4 hours prior to the serum chemistry sample is taken.

i: For anuric patients, urinalysis may not be performed.

j: Coagulation parameters (activated partial thromboplastin time [aPTT], prothrombin time [PT], and international normalized ratio [INR]).

k: The dialysate sample will be taken at 30 minutes and at 3 hours after the start of hemodialysis. The dialysate will be freeze and sent to Aronora.

l: To be performed when the dialyzer cartridge is removed and collected at the end of HD.

m: To be performed prior to dosing.

n: A single dose of xisomab 3G3 or matching placebo will be administered at Hour 0. The dose will be injected through a port into the flowing arterial blood in the proximal dialysis line according to the randomization schedule, immediately after the start of HD.

o: When the PK or PD sample is on an HD day, the sample should be taken at least 1 hour prior the start of HD session. The actual time will be recorded.

p: To be performed at discharge or early termination; the PK and aPTT should be taken at 120 hour postdose.

q: The vascular access sites (AV fistula or AV graft puncture sites) are to be evaluated immediately after the end of HD and removal of the needles from the fistula or graft for bleeding cessation or other reactions.

r: All patients who received the study drug or placebo (including patients who terminate the study early) will undergo follow-up procedures at the Clinical Research Unit (CRU) approximately 12 days after dosing, as they return for their last HD. Events performed on Day 12 can performed at end of HD if more appropriate.

s: Platelet count, BUN and potassium, and aPTT value will be taken from the hematology, serum chemistry, and coagulation sample, respectively, when these are scheduled to be collected at the same time. Samples will not be taken twice at a same timepoint.

Abbreviations: ♀ = Females, AE = Adverse events, BUN = Blood urea nitrogen, BP = Blood pressure, C-I = Check-in, Chem = Chemistry, ConMeds = Concomitant medication, CRU = Clinical research unit, ECG = Electrocardiogram, FSH = Follicle-stimulating hormone, FU = Follow-up, Hem = Hematology, HD = Hemodialysis, HIV = Human immunodeficiency virus, HR = Heart rate, Kt/V = ratio of volume of fluid completely cleared of urea PD = Pharmacodynamic, PK = Pharmacokinetics, PMP = Postmenopausal, RR = Respiratory rate, T = Temperature, UA = Urinalysis URR = Urea reduction ratio.

7 ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC%extrap	Percent of AUC0-inf extrapolated
AUC0-t	Area under the concentration-time curve, from time 0 to the last observed non-zero concentration (t)
AUC0-inf	Area under the concentration-time curve, from time 0 extrapolated to infinity
bpm	Beats per minute
BMI	Body mass index
°C	Degrees Celsius
CFR	Code of Federal Regulations
CI	Confidence interval
CL	Apparent total plasma clearance after oral (extravascular) administration
Cm	Centimeter
Cmax	Maximum observed concentration
CRF	Case report form
CRU	Clinical Research Unit
CS	Clinical significant
CV	Coefficient of variation
ECG	Electrocardiogram
ESRD	End stage renal disease
FDA	Food and Drug Administration
FIH	First in Human
FSH	Follicle-stimulating hormone
FXI	Factor XI
FXIa	Activated FXI
FXII	Factor XII
FXIIa	Activated FXII
G	Gram

GCP	Good Clinical Practice
GLP	Good Laboratory Practice
h	Hour
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HD	Hemodialysis
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IL	Interleukin
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous
Kel	Apparent terminal elimination rate constant
Kg	Kilogram
L	Liter
LS	Least squares
m^2	Meters squared
MedDRA®	Medical Dictionary for Regulatory Activities®
mg	Milligram
mL	Milliliter
mmHg	Millimeter of mercury
MRT	Mean residence team
msec	Millisecond
N	Sample size
No.	Number
PBMC	Peripheral blood mononuclear cells
PD	Pharmacodynamics
PI	Principal Investigator

PK	Pharmacokinetic(s)
PT	Prothrombin time
QA	Quality Assurance
QTc	Corrected value of the interval between the Q and T waves on the electrocardiogram tracing
SAE	Serious adverse event
SAP	Statistical analysis plan
TEAE	Treatment emergent adverse event
Tmax	Time to reach maximum observed concentration
t½	Apparent terminal elimination half-life
URR	Urea reduction ratio
US	United States
USA	United States of America
Vz	Apparent volume of distribution during the terminal elimination phase after oral (extravascular) administration
WHO	World Health Organization

8 INTRODUCTION

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and applicable regulatory requirements. The study population will be comprised of adult male and/or female patients with end stage renal disease.

A brief overview of available information regarding xisomab 3G3 follows below. Details can be found in the xisomab 3G3 Investigator's Brochure (IB 2018).

8.1 Background

Xisomab 3G3 is a novel, injectable, therapeutic recombinant humanized IgG4 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 (F) XII on negatively charged surfaces. Activated FXII (FXIIa) then activates FXI 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 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, including FIX. 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 of 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 has not been determined.

8.2 Nonclinical Studies

8.2.1 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 FeCl3-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 other antithrombotics, currently marketed or under development, that target the functionality of coagulation cascade components downstream of FXII and important for both thrombosis and normal hemostasis, xisomab 3G3 is designed to prevent or treat thrombosis by selectively interfering with the interaction of FXII and FXI, thereby without impeding hemostasis.

8.2.2 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 (Cmax/Dose) was 19.66 ± 0.56 L/kg, the area under the concentration time curve from time 0 to the last time point measured postdose normalized to dose (AUC0-xh/Dose) was 1594 ± 82 kg x h/L, and the apparent volume of distribution (Vd) was 0.050 ± 0.0012 L/kg. Group mean terminal elimination half-lives (t½) 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 t½, CL and Vd 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 t½ were longer and ranged from 61.4 to

248 hours. Individual CL and Vd were estimated between 0.142 and 0.535 mL/h/kg and 34.0 and 57.8 mL/kg, respectively. Intravenous 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 t½ for the males and females at the 50 mg/kg dose level was 155 hours and 185 hours, respectively. The average volume of distribution (Vd) was 45.2 mL/kg and 45.3 mL/kg for the males and females, respectively and the clearance (CL) was 0.202 and 0.170 mL/h/kg for the males and females, respectively.

8.2.3 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 tested and 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 postdose (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 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.

8.3 Clinical Studies

A first-in-human (FIH) study (Study No. 3G3-15-01 [Celerion Project No.: CA19214]) was completed in the United-States on January 16, 2018. This study was a single ascending dose study in healthy adult male and female subjects with the purpose of collecting safety, tolerability, PK, and PD information in order to support further development of xisomab 3G3. 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]) were dosed. Subjects received a single IV infusion (less than 5 minutes) of 0.1 mg/kg (Cohort 1), 0.5 mg/kg (Cohort 2), 2 mg/kg (Cohort 3), or 5 mg/kg (Cohort 4) xisomab 3G3 or placebo.

A total of 21 subjects entered the study, received the study medication or placebo, and completed the study per protocol. Below is a summary of the preliminary data from this FIH study as of 07 of May 2018.

8.3.1 Safety Data

There were no deaths or SAEs experienced in this study. No subjects were discontinued due to AEs. Overall, 10 (48%) of 21 subjects experienced a total of 20 TEAEs in this study, with 7 (44%) of 16 subjects following active treatment and 3 (60%) of 5 subjects following placebo. The highest incidence of TEAEs by system organ class was skin and subcutaneous tissue disorders, experienced by 3 (19%) active-treatment subjects and 1 (20%) placebo subject. The most common TEAE in this study was productive cough, considered unrelated or unlikely treatment related and experienced by 2 (13%) active treatment subjects. All other TEAEs were experienced by 1 subject. The majority of events (17) were mild (Grade 1) in severity and 3 were moderate (Grade 2). Moderate events included increased diastolic BP (2 mg/kg xisomab 3G3), productive cough (5 mg/kg xisomab 3G3), and upper respiratory tract infection (0.5 mg/kg xisomab 3G3). As expected, increases from baseline in aPTT were noted following all treatments, with greater magnitude and duration of these increases following administration of the higher doses of xisomab 3G3.

A single IV dose of xisomab 3G3 up to 5 mg/kg appeared to be safe and generally well tolerated by the healthy male and female subjects in this study.

8.3.2 Pharmacokinetics and Pharmacodynamics Data

The plasma xisomab 3G3 PK profiles were best characterized at the 5 mg/kg dose level. The PK profiles and PK parameters in the 0.1 mg/kg dose level were not well characterized since the majority of concentrations fell below the LLOQ; thus, an insufficient number of time points were available to characterize the elimination phase from 3 out of 4 subjects at that dose level. Terminal phase PK may have not been reliable at the doses below 5 mg/kg, noting that Vss appeared to be underestimated (were less than physiological blood volumes), and that half-life estimations increased when xisomab 3G3 was quantifiable for longer intervals.

Plasma xisomab 3G3 exposure (AUCs and Cmax) increased with increasing dose levels. Although a dose proportionality analysis was not performed in this study, the mean PK parameter values indicated that plasma xisomab 3G3 exposure appeared to increase in a slightly more than dose-proportional manner from 0.5 to 5 mg/kg. The PK parameters calculated from the 0.1 mg/kg dose were less robust as most parameters were estimated in only 1 subject due to the absence of an observable elimination phase in 3 out of 4 subjects. The maximal concentrations peaked early, with Tmax values achieved before 1 hour following start of infusion. Elimination of the drug was decreased with increasing xisomab 3G3 doses, as shown by a lower Kel, longer t½, and lower CL. A summary of mean PK parameters and mean concentration profile can be found in Table 1 and Figure 1.

Table 1: Key PK Parameters

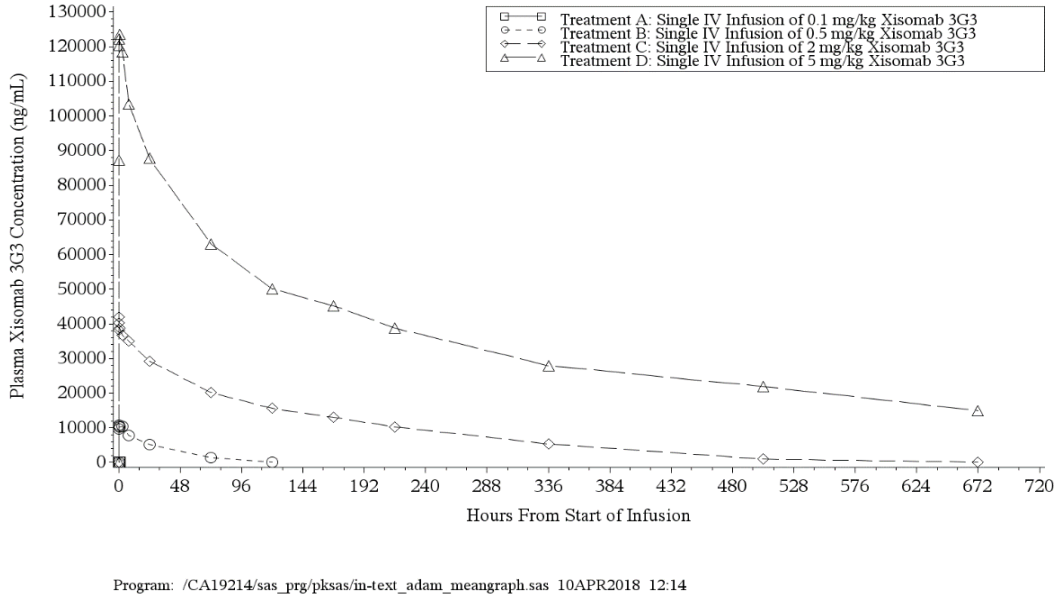
	Dose			
Parameters (units)	**0.1 mg /kg**	**0.5 mg/kg**	**2 mg/kg**	**5 mg/kg**
N	3*	4	4	4
AUC0-t (ng•h/mL)	60.47 ± 38	368 500 ± 23	5 657 000 ± 24	28 270 000 ± 12
AUC0-inf (ng•h/mL)	-	370 400 ± 23	5 668 000 ± 24	28 290 000 ± 12
Cmax (ng/mL)	124.9 ± 23	11 250 ± 9	42 750 ± 12	127 300 ± 3
Tmax (h)	0.084 ± 2.4	1.15 ± 113	0.13 ± 65	1.01 ± 132
t½ (h)	-	16.638 ± 9	60.63 ± 7	121.49 ± 85
CL (L/h)	-	0.09 ± 20	0.026 ± 13	0.014 ± 23
Vss (L)	-	2.52 ± 24	3.72 ± 11	4.31 ± 18

AUC = area under the concentration-time curve; CL = apparent body clearance; Cmax = maximum observed plasma concentration; N = number of subjects; CV% = coefficient variation; t½= elimination half-life; Tmax = time of observed Cmax; Vss = apparent volume of distribution.

Data presented as mean ± CV%

* Non-zero concentration data from only 3 of 4 subjects was available for PK analysis.

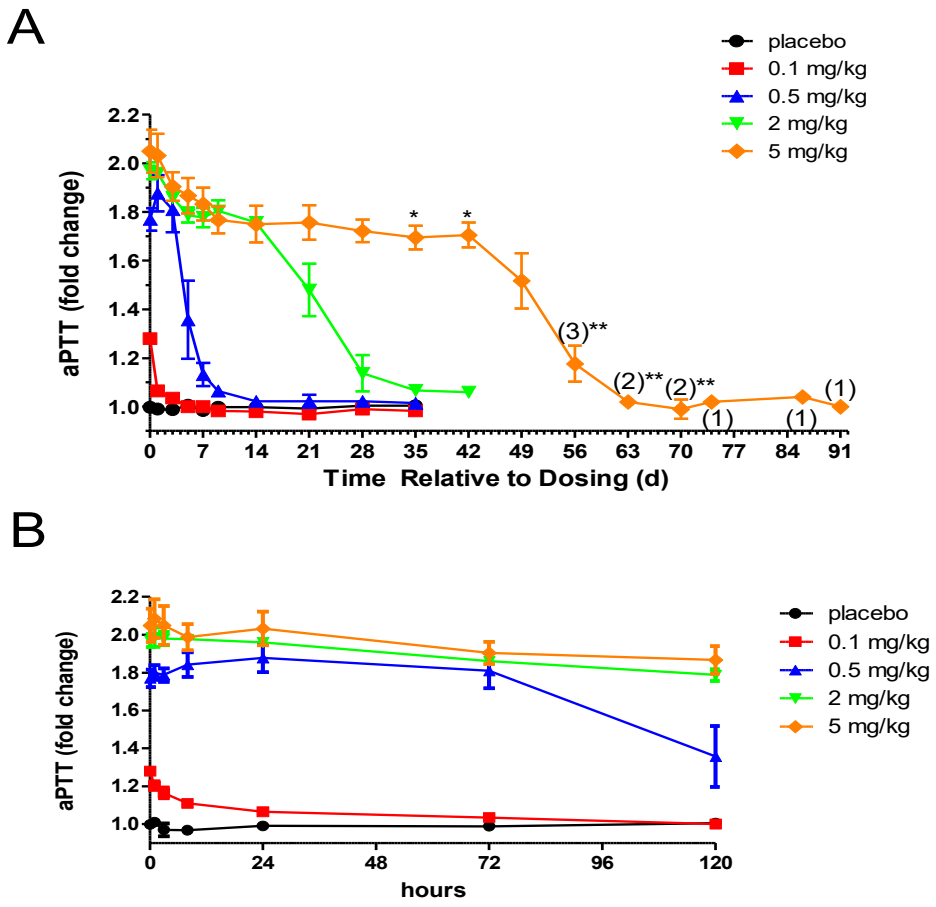
Figure 1: Mean Concentration Profile



Program: /CA19214/sas_prg/pksas/in-text_adam_meangraph.sas 10APR2018 12:14

aPTT was prolonged in all cohorts after xisomab 3G3 IV administration, and near-saturation of the effect was observed around the 0.5 mg/kg dose. Results showed that the maximum aPTT values achieved increased with increasing xisomab 3G3 dose levels, and the aPTT values decreased towards baseline values over time as depicted in Figure 2. The time for aPTT to return to baseline (±10%) increased as the dose levels increased. This may be correlated to a slower in elimination rate of xisomab 3G3 from the plasma as the doses increased.

Figure 2: Mean aPTT Profile Over Time



Legend:

(A) aPTT of Cohorts 1 to 4 for the duration of the Phase 1 clinical trial to date in days (d)

(B) aPTT data from the first 120 hours (h) post-dose.

Numbers in parentheses indicate the number of subjects at that time point. *blood sample taken within 24 hours of time point indicated. **blood sample taken within 48 hours of time point indicated.

8.4 Rationale

8.4.1 Rationale for this Study and Study Design

A FIH study was conducted in healthy subjects and concluded that a single dose of xisomab 3G3 up to 5 mg/kg was safe and generally well tolerated. Results also confirmed that xisomab 3G3 prolonged aPTT values; the magnitude and duration of which were dose-related. This study will explore the potential utility of single infusion doses of xisomab 3G3 in ESRD patients who are on chronic HD.

Thromboembolic disease and bleeding are common comorbidities in subjects with chronic kidney diseases (Lutz et al., 2017). In most ESRD patients, heparin is routinely used during outpatient HD to reduce clotting in the dialyzer cartridge and to improve HD efficiency. However, administration of heparin during HD temporally increases the risk of bleeding. A safe alternative for patients with active bleeding, or that are at a high risk for bleeding complications, is heparin-free dialysis (Schwab et al., 1987; Stamatiadis et al., 2004; and Caruana et al., 1987) and the majority of HD patients that are admitted to the hospital are routinely dialyzed without heparin due to bleeding concerns.

In this study design, subjects will be confined to the clinic for the majority of the trial and will not receive heparin during their HD sessions. While heparin-free HD can increase clotting within the dialyzer, resulting in the need for exchange of the dialyzer cartridge during HD in 5-7% of the procedures (Cronin and Reilly, 2010), there is no evidence that HD without heparin results in increased thromboembolic complications. Indeed, heparin anticoagulation during HD is not intended for systemic thromboprophylaxis and a recent retrospective analysis of data from the United States Renal Data System and electronic medical records shows that heparin-free HD is not associated with increased risk of thromboembolic events in ESRD patients (Shen et al., 2013). Therefore, the removal of standard of care heparin anticoagulation in either arm for the short duration of the study is not expected to place the patients at an increased risk for development of thromboembolic complications, and additionally enables the most rigorous assessment of safety and efficacy for xisomab 3G3 that would not be possible if heparin treatment was maintained.

Xisomab 3G3 is expected to prevent pathologic thrombogenesis by selectively inhibiting thrombotic contact pathway activation without interrupting normal hemostasis or the hemostatic feedback activation of FXI by thrombin, or other mechanisms. As both thromboembolism and bleeding are common comorbidities in ESRD patients, safe anticoagulation is currently an unmet need for this patient population. Xisomab 3G3 is a fundamentally novel anticoagulant that is expected to reduce clot formation in vascular devices, including the hemodialyzer apparatus, without the increased risk of bleeding associated with heparin. In addition, data to date suggest that xisomab 3G3 may also reduce the incidence and severity of thromboembolic events in these patients. Further, non-clinical data suggest that xisomab 3G3 reduces systemic inflammatory responses, which may be detrimental, and has been associated with contact activation of the blood that is perfused through devices during external organ support. As such, xisomab 3G3 stands as a promising alternative to other anticoagulants in this population. It is therefore of interest to assess xisomab 3G3 safety and effectiveness in ESRD patients on chronic HD.

A placebo arm is included in this study design in order to robustly demonstrate the safety and efficacy of xisomab 3G3 while not placing the subjects at unnecessary risk, as mentioned above. The primary endpoint in this study is safety, measured as the number of adverse events that occur during the observation period. A heparin free inpatient HD observation period (Study Days -7 to 1) is included in the trial design to establish a baseline for the heparin-free procedure. Continuation of the heparin-free HD procedure during the subsequent trial period and inclusion of a placebo arm allows for the determination of whether an adverse event is drug-related or not and permits accurate assessment of the safety of the study drug. The addition of a placebo arm also removes potential bias from the interpretation of AEs by the PIs and the subjects. The secondary endpoint for this study is efficacy of xisomab 3G3 on hemodialysis efficiency which may be more clearly observed with a placebo control instead of an active control (e.g., heparin). While the placebo arm may be at the same risk of clotting within the dialysis circuit as during the pre-dosing period (Study Days -7 to 1), data cited above suggests that these patients will not be at higher risk for either thromboembolic or bleeding complications. Should clotting occur within the dialyzer cartridge during a hemodialysis session that results in dialyzer failure, the dialyzer cartridge will be replaced, and the patient will be closely monitored by the PI. It is important to note that replacement of the dialyzer cartridge during HD is safe for the patient and a routine procedure in cases of dialyzer failure.

8.4.2 Rationale for the Dose Selection

Doses of 0.25 mg/kg and 0.5 mg/kg were selected for this phase 2 study in order to provide adequate PD and PK characterization but still allowing a safety margin should the results differ in this population compared to healthy subjects. The 0.25 mg/kg xisomab 3G3 dose is 2.5-fold higher than the lowest dose in the FIH study. The 0.1 mg/kg dose in the FIH study had a short and modest, yet detectable PD effect (several seconds of temporal aPTT prolongation). The 0.25 mg/kg dose is expected to provide an initial plasma concentration that is within the range of average FXI concentration, the molecular target of xisomab 3G3, in human subjects, and may approach saturation in some individuals after full distribution. Therefore, it has the potential to exert brief pharmacological (anti-inflammatory, antithrombotic) activity, possibly lasting up to a day, until elimination of the antibody and hepatic FXI secretion that neutralizes the antibody.

The 0.5 mg/kg dose was safely administered in the FIH study and allowed adequate characterization of the PK profile in healthy adults. In addition, following a 0.5 mg/kg a prolongation of aPTT was seen, with highest values measured at 24 hours postdose and having a sustained effect for at least 72 hours postdose. The 0.5 mg/kg xisomab 3G3 dose is expected to provide, after complete distribution, a plasma concentration that is approximately twice the average human plasma concentration of the FXI antigen. Therefore, this dose is expected to be overcome by FXI generation later, and have pharmacological activity that lasts longer than the lower dose level.

8.5 Risks and/or Benefits to Patients

ESRD patients are often ill, and are prone to a variety of adverse events on or off HD, ranging, for example, from infections to hypertension to bleeding to thromboembolism to acute ischemic cardiovascular emergencies, even if they are apparently stable on chronic HD. A temporal and modest increase in blood pressure was observed in one study subject in the FIH study after xisomab 3G3 administration, and the event was deemed potentially related to the study drug.

Xisomab 3G3 is a purified protein produced by recombinant DNA technology in a mammalian cell culture system, and these types of drugs can, occasionally and unpredictably evoke acute allergic reactions. Some ESRD patients develop chronic HD- and uremia-related moderate hemorrhagic diathesis or hemostasis impairment. Even though currently available data do not indicate a hemostatic function for the FXI/FXII interaction, there remains a theoretical possibility of contact activation-mediated enhancement of hemostasis. Thus, the hemostatic safety of xisomab 3G3 in the complex conditions of ESRD and chronic HD is not yet known. The safety monitoring practices employed by this protocol (i.e., 12-lead ECG, vital signs, blood pressure, clinical laboratory tests, AE questioning, vascular access site (AV fistula or AV graft) monitoring, and physical examination) are adequate to protect the patients' safety and should detect all expected and unexpected treatment-emergent AEs (TEAEs). In addition, the cohorts will be dosed in a sequential manner, starting with the lower dose level, Cohort 1.

Patients undergoing heparin-free HD may be at higher risk of developing clots within the hemodialyzer. Should this occur, site standard operating procedures will be followed to replace the clotted dialyzer and resume HD under the supervision of the PI. It is important to note that replacement of the dialyzer cartridge is a safe procedure for the patient. While studies suggest that there is no risk of thromboembolic complications should this occur, clotting of the dialyzer circuit could result in up to ~228 mL of blood loss.

There may be direct health benefit for study participants from receipt of study drug, some evaluated among the secondary outcome measures. Xisomab 3G3 and its murine precursor, 14E11, have shown anti-inflammatory and antithrombotic effects in non-clinical studies. Both inflammatory responses to exposure of blood to the foreign surfaces of the HD equipment, and thrombus formation-related consumption of blood components, anywhere in the body, or thrombus layer entrapment in the dialyzer equipment, especially in the absence of systemic anticoagulation with heparins, may be reduced in the presence of pharmacologically active levels of xisomab 3G3. Reduced thrombus accumulation on the dialyzer surface may potentially improve the efficiency of hemodialysis as well. An indirect health benefit for study participants enrolled in this study is the free medical tests received at screening and during the study.

9 OBJECTIVES AND ENDPOINTS

9.1 Objectives

The primary objective of this study is:

- To assess the safety and tolerability of a single dose of xisomab 3G3 when injected through a port into the proximal (arterial) dialysis line immediately after initiation of a HD procedure in patients with ESRD.

The secondary objectives of this study are:

- To assess the PD of a single dose of xisomab 3G3 when injected through a port into the proximal (arterial) dialysis line immediately after initiation of a HD procedure in patients with ESRD.
- To assess the efficacy of a single dose of xisomab 3G3 on HD efficiency when injected through a port into the proximal (arterial) dialysis line immediately after initiation of a HD procedure in patients with ESRD.
- To assess the PK of a single dose of xisomab 3G3 when injected through a port into the proximal (arterial) dialysis line immediately after initiation of a HD procedure in patients with ESRD.

9.2 Endpoints

Primary outcome measures:

- The safety and tolerability of xisomab 3G3 will be evaluated versus pre-treatment and placebo by reviewing number and severity of adverse events and use of concomitant medications, physical examination, vascular access site reaction, bleeding time, and changes in vital signs, ECGs, and clinical laboratory evaluations.

Secondary outcome measures:

- PD using dose-dependency of drug potency, determined by measuring changes in coagulation parameters, and thrombus accumulation (assessed and ranked by visual inspection) within the dialyzer cartridges and total protein accumulation in the HD filter after xisomab 3G3-treatment versus pre-treatment and placebo.

- Efficacy on hemodialysis efficiency using BUN and potassium levels before and after hemodialysis, length of HD, measurement of urea removed by 3 hours of dialysis, and total dialysate urea (single pool Kt/V and URR) after xisomab 3G3-treatment versus pre-treatment and placebo.

Other outcome measures:

- PK parameters of xisomab 3G3, calculated, as appropriate: AUC0-t, AUC0-inf, AUC%extrap, Cmax, Tmax, Kel, t½, CL, and Vss.
- Development of immunity or antibodies against xisomab 3G3 after drug exposure.

10 STUDY DESIGN

10.1 Overall Study Design and Plan

This is a phase 2, randomized, double-blind, placebo-controlled, single-dose study of xisomab 3G3 designed to evaluate the safety, efficacy/potency, and PK at 2 dose levels administered to patients with ESRD undergoing HD.

A total of up to 24 adult male and female patients will be enrolled; 9-12 patients are planned for each cohort. In each cohort, an attempt will be made to enroll at least 50% of females and at least 30% of a race/ethnicity minority group. Patients will be enrolled into Cohort 1 or Cohort 2; cohorts will be dosed sequentially. Within a cohort, patients will be randomized to active drug or placebo as summarized below:

Table 2: Cohort and Treatment Randomization

Cohort	Treatment	Active:Placebo	Cohort Size
1	Infusion dose of 0.25 mg/kg xisomab 3G3 or placebo	2:1	9-12
2	Infusion dose of 0.5 mg/kg xisomab 3G3 or placebo	2:1	9-12

This study includes a screening period of 28 days prior to checking-in to the clinical research unit on Day -8. From Day -7 (one week prior to dosing on Day 1) through Day -1, all patients will undergo HD 3 times and will be assessed for all scheduled procedures and endpoints before and after each HD session as per the Study Events Flow Chart (Section 6).

On Study Day 1, prior to dosing, patients will undergo baseline measurements followed by initiation of a regular HD procedure, consistently using only one type of dialyzer cartridge in each patient. Immediately after the start of blood perfusion, a single dose of xisomab 3G3 or matching placebo will be injected through a port into the flowing arterial blood in the proximal dialysis line. Patients will continue to undergo HD procedures and scheduled assessments from Day 1 through Day 12.

Study assessments will include physical examinations, vital signs, ECGs, clinical laboratory tests, HD vascular access site (AV fistula or AV graft) reaction, antibody titer (immunogenicity), AEs, PD blood sampling (coagulation parameters), and PK blood sampling to be performed throughout the study according to the Study Events Flow Chart (Section 6). On Days -7, -5, and -3 and Days 1, 3, 5, and 12, bleeding time from the HD vascular access sites on the AV fistula or AV graft (ladder or buttonhole technique) will be evaluated at the end of the HD session. The dialyzer cartridge will be rinsed and visually inspected at the end of the HD procedure and graded against a standardized visual assessment scale. After visual assessment, the used and rinsed dialyzer cartridge will be frozen and saved for later retained content (deposited blood-derived material) analysis. The number of dialyzer cartridges used for the HD session will be recorded.

Patients who withdraw prematurely from the study may be replaced at the discretion of the Investigator and Aronora, Inc. to ensure that up to 24 patients (9 to 12 patients per cohort) complete the study.

10.1.1 Confinement and Follow-Up

Patients will be housed on Day -8, at the time indicated by the CRU, until after completion of study procedures on Day 6 as indicated in the Study Events Flow Chart (Section 6). Patients will return to the CRU as per the Study Events Flow Chart (Section 6) for additional HD sessions and study procedures. At all times, a patient may be required to remain at the CRU for longer at the discretion of the Principal Investigator (PI) or designee.

All patients who received the study drug or placebo (including patients who terminate the study early) will undergo follow-up procedures at the CRU approximately 12 days after dosing.

10.1.2 End of Study Definition

The end of study is defined as the date of the last scheduled study procedure as outlined in the Study Events Flow Chart (Section 6).

11 STUDY POPULATION

11.1 Inclusion Criteria

Patients must fulfill all of the following inclusion criteria to be eligible for participation in the study:

1. ESRD maintained on stable outpatient HD regimen, using an established (> 3 months) and normally functioning, regular flow, uninfected first mature AV fistula (or AV graft) and skin consistent with standard chronic HD access injuries, and HD stability defined as Kt/V ≥ 1.2 within 3 months prior to screening at a healthcare center for > 3 months from screening.

2. On HD regimen at least 3 times per week for a minimum of 3 hours per dialysis session, using a complication-free well maintained AV fistula (or AV graft), expected and plan to continue this throughout and for at least 3 months beyond the study.

3. Is capable of understanding the written informed consent, provides signed and witnessed written informed consent, and agrees to comply with protocol requirements and study-related procedures.

4. Willing to be confined to the CRU for the duration of the study, able to comply with all study-related requirements, and able to adhere to study restrictions and visit schedules.

5. Male or female, between 18 and 80 years of age (inclusive) at the time of screening.

6. BMI of ≥ 18 at the time of screening.

7. Considered by the PI to be clinically stable with respect to underlying ESRD, based on medical evaluation that includes medical and surgical history, and a complete physical examination including vital signs, ECG, and clinical laboratory test results at screening. Repeat assessments are permitted for any laboratory, ECG, or vital sign parameter required for enrollment.

8. Female patients must be of non-childbearing potential and 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. Male patients must either be sterile (vasectomy with history of a negative sperm count following the procedure); practice total abstinence from sexual intercourse as the preferred lifestyle (periodic abstinence is not acceptable); use a male condom with any sexual activity; or agree to use a birth control method considered to be appropriate by the Investigator (such as one of the methods identified above for female patients) from the time of screening until 90 days after study drug administration. Male patients must agree not to donate sperm for a period of 90 days after study drug administration.

11.2 Exclusion Criteria

Patients must not be enrolled in the study if they meet any of the following criteria:

1. Documented history of acute vasoocclusive thrombotic event (acute coronary syndrome, stroke or transient ischemic attack, venous thromboembolic event), or vascular access fistula or AV graft failure in the past 3 months.

2. With the exception of unfractionated heparin during HD, concomitant or prior use of anticoagulant/antiplatelet agents (e.g., low molecular weight heparins, warfarin, apixaban, bivalirudin, ticagrelor, edoxaban, dabigatran, rivaroxaban, clopidogrel, prasugrel, ticlopidine, eptifibatide, tirofiban, dipyridamole, diclofenac, and all other NSAIDs) that may affect hemostasis for 2 weeks prior to check-in on Day -8 and throughout the study.

3. Use of unfractionated heparin for HD sessions from check-in on Day -8 and throughout the study.

4. Any clinically significant (CS) concomitant disease or condition (including treatment for such conditions) that, in the opinion of the PI, could either interfere with the study drug, compromise interpretation of study data, or pose an unacceptable risk to the patient.

5. Any other CS abnormalities in laboratory test results at screening that would, in the opinion of the PI, increase the patient's risk of participation, jeopardize complete participation in the study, or compromise interpretation of study data.

6. Pregnant (positive pregnancy test) at screening or check-in on Day -8. If serum human chorionic gonadotropin (hCG) pregnancy test results are indeterminate, follow-up testing should be performed to determine eligibility.

   All female patients will not be pregnant and will have a negative pregnancy test at screening and check-in on Day -8, with the following exception: females receiving dialysis with an indeterminate pregnancy test result or persistently low hCG resulting in a false positive pregnancy test may be included in the study at the discretion of the PI. Postmenopausal patients with a result outside the postmenopausal range or an indeterminate pregnancy test will undergo additional testing with FSH to confirm postmenopausal status prior to study enrollment.

7. Treatment with another investigational drug or device study within 30 days (or 5 half-lives, whichever is longer) prior to check-in on Day -8.

8. Acute illness that is considered by the PI to be CS within 2 weeks of check-in on Day -8.

9. Currently have established underlying inherited or acquired symptomatic bleeding disorders and/or are at risk for excessive bleeding per PI judgment or current active bleeding (e.g., gastrointestinal, intracranial), aside from minor bleeding from the puncture site on the AV fistula or AV graft, which would be expected to occur during the dialysis procedure, with the following values:

   - Platelet count < 100,000 cells/mm^3 (if < 100,000 but > 75,000 cells/mm^3, with permission of PI and medical monitor) at screening
   - INR > 1.4 at screening
   - aPTT up to 1.2 x ULN (if >1.2x ULN up to < 1.5 x ULN, with permission of PI and medical monitor) at screening
   - ALT or AST > 2 x ULN at screening
   - Total bilirubin > 1.2 ULN at screening
   - Hemoglobin concentration < 10 g/dL at screening

10. Seated blood pressure < 90/40 mmHg at screening and check-in on Day -8.

11. Exclusion criteria for ECG at screening and check-in on Day -8:

Heart rate	< 45 and > 110 bpm
QTcF interval	> 500 msec
bpm = beats per minute; msec = milliseconds; QTcF = QT interval corrected using Fridericia's formula	

   - Any significant arrhythmia or conduction abnormality, (including but not specific to atrioventricular block [2nd degree or higher], Wolff Parkinson White syndrome [unless curative radio ablation therapy]), which, in the opinion of the PI and Medical Monitor, could interfere with the safety for the individual patient.
   - Non-sustained or sustained ventricular tachycardia (> 2 consecutive ventricular ectopic beats at a rate of > 1.7/second).

12. History of a CS allergy to recombinant biologic drug, rodents, or a known sensitivity or idiosyncratic reaction to any compound present in xisomab 3G3, its related compounds, or any compound listed as being present in the study formulation.

13. Participate in strenuous exercise from 48 hours prior to check-in on Day -8 and throughout the study.

14. Positive test for drugs of abuse and/or positive alcohol test at screening or check-in on Day -8 if not accounted for by a prescription medication. Patients with a positive test based on a prescribed medication may be enrolled.

15. Positive test at screening for hepatitis B surface antigen (HBsAg) or human immunodeficiency virus (HIV). If a patient with ESRD has positive test results for hepatitis C virus (HCV) but liver function tests are otherwise not clinically significant, the patient may be included at the PI's discretion.

16. Receiving blood purification therapy other than HD.

17. Any other reason that would render the patient unsuitable for study enrollment at the discretion of the PI.

11.3 Early Termination of Patients from the Study

Patient participation in this study may be discontinued for any of the following reasons:

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

2. If the patient clots the hemodialyzer twice they may be discontinued from the study at the discretion of the PI. If the patient fully clots the hemodialyzer, continuation of the patient in the study will be at the PIs discretion.

3. 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 patient.

4. Patient's decision to withdraw.

5. Requirement of prohibited concomitant medication.

6. Patient failure to comply with protocol requirements or study related procedures.

7. Termination of the study by the Sponsor, FDA, Celerion, CRU, or other regulatory authorities.

The clinical report will include reason(s) for patient withdrawals as well as details relevant to the patient withdrawal.

If a patient is withdrawn from the trial prior to study completion, the patient will undergo all procedures scheduled for early termination as the situation allows (see the Study Events Flow Chart (Section 6). Any patient 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.

11.4 Study Restrictions

11.4.1 Prohibitions and Concomitant Medication

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

- Xanthines/caffeine: 48 hours prior to dosing and throughout the period of sample collection (small amounts of caffeine derived from normal foodstuffs e.g., 250 mL/8 oz./1 cup 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 prior to dosing and throughout the period of sample collection;

Concomitant medications will be listed, recorded, and allowed except for those listed as prohibited in the exclusion criteria in Section 11.2. It is understood and will be considered that treatment with certain drugs or cessation of treatment with certain drugs (e.g., drugs for hypertension) may have adverse effects and could interfere with the evaluation of the primary outcome measures of the study.

After randomization, acetaminophen (up to 2 g per 24 hours) may be administered, for fever or chronic pain control, at the discretion of the PI or designee. Administration of opioids for certain types of pain management may be allowed.

If deviations occur, the PI or designee in consultation with the Sponsor if needed will decide on a case-by-case basis whether the patient may continue participation in the study.

11.4.2 Meals

At the CRU, meals and/or snacks and fluids will be provided at appropriate times following check-in and throughout the study as per the clinical site standard procedure.

11.4.3 Activity

On Day 1, as dosing will be immediately after the start of the hemodialysis session, patients will be dosed in the same position as required for their hemodialysis session. Patients will maintain that position for the whole hemodialysis session, as per standard HD procedure, except when they are supine or semi-reclined for other study procedures. At other times, there will be no specific activity restrictions. However, should AEs occur at any time, patients may be placed in an appropriate position.

Patients will be instructed to refrain from strenuous exercise which could cause muscle aches or injury, including contact sports at any time from 48 hours prior to check-in on Day -8 and throughout the study.

12 TREATMENTS

12.1 Treatments Administered

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

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

Investigational materials will be provided by the Sponsor as in Table 3.

Table 3: Identity of Investigational Products

Product	Description
Test	Lyophilized xisomab 3G3 (~15 mg/mL) sterile powder for injection in formulation buffer (8% sucrose, 10 mM histidine, 30 mM arginine HCl, 10 mM methionine, 80 ppm polysorbate 80, pH 5.4)
Placebo	Lyophilized formulation buffer (8% sucrose, 10 mM histidine, 30 mM arginine HCl, 10 mM methionine, 80 ppm polysorbate 80, pH 5.4)

An unblinded pharmacist will be responsible for providing xisomab 3G3 or placebo to the blinded study personnel for administration via injection into the proximal hemodialysis line as per the randomization scheme.

Patients will be enrolled into Cohort 1 or Cohort 2. Within a cohort, patients will be randomized to active drug or placebo as summarized in Table 2.

Patients will receive a single infusion dose of 0.25 mg/kg xisomab 3G3, 0.5 mg/kg xisomab 3G3, or matching placebo on Day 1 at Hour 0. The dose will be administered proximal to the dialyzer cartridge, into the arterial line immediately after start of HD.

Hour 0 will correspond to the start of the xisomab 3G3 infusion. The time at which the infusion is started and stopped must be recorded.

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

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.

12.2 Dose Modification

The dose and administration of the study drug to any patient within a cohort may not be modified. If necessary, a patient must be discontinued for the reasons described in Section 11.3.

12.3 Method of Assigning Patients to Treatment Groups

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

Patients will be enrolled to Cohort 1 or Cohort 2 with Cohort 1 conducted prior initiation of Cohort 2. In each cohort, an attempt will be made to enroll at least 50% of females and at least 30% of a race/ethnicity minority group. An attempt will also be made to approximately match key characteristics, including sex, average age, and weight per cohort.

In each cohort, patients will be randomized to receive either xisomab 3G3 or placebo maintaining a 2:1 ratio

If replacement patients are used, the replacement patient number will be 100 more than the original (e.g., Patient No. 101 will replace Patient No. 1).

12.4 Blinding

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

12.4.1 Maintenance of Randomization

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

12.4.2 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 patient.

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 patient only. In the event that the emergency is one, in which it appears that the other patients may be at imminent risk, the blind may be broken for all patients 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.

12.4.3 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, CRFs signed by the PI, and the database is officially locked.

12.5 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 patient has received the entire dose. In the case of an incomplete dosing a few milliliters of blood could be drawn back into the dosing syringe and carefully reinjected to ensure administration of the complete dose; this will be reported.

13 STUDY ASSESSMENTS AND PROCEDURES

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 patient 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, vascular access site reaction, 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.

13.1 Screening

Within 28 days prior to check-in on Day -8, medical history and demographic data, including name, sex, age, race, ethnicity, body weight (kg), height (cm), BMI (kg/m^2) and history of tobacco use will be reported. Each patient will have a physical examination, vital sign measurements (heart rate, blood pressure, temperature, and respiratory rate), 12-lead ECG, and the laboratory tests of hematological, coagulation, hepatic and renal function and additional tests as noted in Section 13.2.7.

13.2 Safety and Tolerability Assessments

13.2.1 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.

13.2.2 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.

Vital signs will be performed with patients in a seated position following a 5 minute rest period, 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.

When scheduled postdose, vital signs will be performed within approximately 15 minutes of the scheduled time point.

13.2.3 ECG 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 patients in a semi-recumbent position following a 5 minute rest period. All ECG tracings will be reviewed by the PI or designee.

When scheduled postdose, ECGs will be performed within approximately 20 minutes of the scheduled time point.

13.2.4 Body Weight

Body weight (kg) will be measured daily up to Day 6, and before and after each HD session, as outlined in the Study Events Flow Chart (Section 6).

13.2.5 Vascular Access Site Reaction Assessment

The monitoring of AEs will pay special attention to vascular access fistula (or AV graft) site reactions. The preferred vascular access is an established AV fistula (or AV graft). Well established and reaction-free AV graft is an alternative, but less preferred access option, as it is more prone to complications. Patients who are hemodialyzed through catheters are not included in the study. Therefore, inspection of the AV fistula (or AV graft) and surrounding area will be performed. Any new abnormal findings inconsistent with past skin injuries as expected in patients on chronic HD will be reported as AEs. AV fistula (or AV graft) site reactions will be evaluated as outlined in the Study Events Flow Chart (Section 6). Prior to HD, the AV fistula (or AV graft) site will be examined for inflammation, infection, or flow abnormalities. When scheduled postdose, injection site examinations will be performed within approximately 20 minutes after completion of the HD session. 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 (FDA Guidance 2007) 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.			

13.2.6 Bleeding of Access Site

Evaluation of bleeding and bleeding time from the HD vascular access sites on the AV fistula or AV graft using the ladder or buttonhole technique will be performed as per Study Events Flow Chart (Section 6).

Following hemodialysis, the needle will be removed from the vascular access site and immediately followed by the placement of the dressing (i.e., gauze). Pressure will be applied manually by a clinical associate for 10 minutes before checking for evidence of bleeding around the dressing. If there is still some bleeding, pressure will be applied back at the site for 5 minutes. The site will then be checked again for evidence of bleeding; this procedure will be repeated every 5 minutes until bleeding has stopped. Once bleeding has stopped, a new gauze dressing is applied and then taped. To ensure consistency when applying the pressure, the clinical staff will have received adequate training and an attempt will be made to have the same associates perform this test.

The time to clot will be recorded.

13.2.7 Clinical Laboratory Tests

All tests listed below will be performed as outlined in the 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 or saliva drug screen
  - Opiates
  - Amphetamines
  - Cocaine
  - Cannabinoids
- Urine, breathalyzer, or saliva alcohol screen
- Serum pregnancy test (for females only)
- FSH (for postmenopausal females only)

* Serum chemistry tests will be performed after at least a 4-hour fast; however, in case of dropouts or rechecks, patients may not have fasted for 4 hours prior to 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.

† For anuric patients, urinalysis may not be performed.

13.2.8 Adverse Events

13.2.8.1 Adverse Event Definition

AE will be defined as any untoward medical occurrence during the study, associated or not with the use of xisomab 3G3 in the study patients, whether or not considered drug related. TEAE is an AE that occurs after administration of the study drug or placebo.

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 study drug. (FDA Guidance, 2012)

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

13.2.8.2 Monitoring

Patients will be monitored for AEs from check-in through completion of the study. Patients 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 serious adverse events (SAEs) will be performed by a licensed medical provider, either at the CRU 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).

13.2.8.3 Reporting

All AEs that occurred during this clinical study (i.e., before, during, and after exposure of ESRD patients to xisomab 3G3) will be recorded. This design is to improve Sponsor ability to obtain reliable initial information about drug safety yet reducing the number of study patients needed to generate useful data.

Adverse events and SAEs that are related to study participation (e.g., protocol-mandated intervention) will be recorded from the time the patient check-in until study completion. All other AEs and SAEs will be recorded from Day -8 until exit from the study.

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 study drug (likely, probably, possibly, unlikely, or unrelated) and severity. 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 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). (FDA Guidance 2007)

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

13.2.8.4 Serious Adverse Event

If any AEs are serious, as defined by the Food and Drug Administration (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. The institutional review board (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 patient on this study, contact the Sponsor personnel listed in Section 3.

13.3 Hemodialysis Procedure and Blood Clots in the Dialyzer Cartridge

Patients will undergo hemodialysis 3 times a week as delineated in the Study Events Flow Chart (Section 6). For each patient, the hemodialysis will last at least 3 hours as per patient standard schedule which will be the same throughout the study.

Patients undergoing heparin-free hemodialysis may be at higher risk of developing clots within the hemodialysis circuit. In order to monitor clotting within the HD circuit, venous pressure will be continuously monitored. Should clotting within the dialyzer occur, site standard operating procedures will be followed to replace the clotted dialyzer and resume hemodialysis under the supervision of the PI, if appropriate. It is important to note that replacement of the dialyzer cartridge is a safe procedure for the patient. While studies

suggest that there is no risk of thromboembolic complications should this occur, clotting of the dialyzer circuit could result in up to ~228 mL of blood loss.

The hemoglobin levels will be followed more closely.

If the patient clots the hemodialyzer twice they may be discontinued from the study at the discretion of the PI. If the patient fully clots the hemodialyzer, the continuation of the patient in the study will be at the PIs discretion.

13.4 Immunogenicity Assessment

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

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

13.5 Pharmacodynamic Assessments

Pharmacodynamic assessment will include evaluation of drug potency and efficiency of HD. For all patients, PD assessments will be performed at scheduled time points as delineated in the Study Events Flow Chart (Section 6).

Drug potency will be evaluated using the following PD markers:

- thrombus accumulation will be evaluated by a visual inspection of the dialyzer membrane at the end of HD procedures and by a gradation using a standardized visual assessment scale (e.g., Ronco et al., 2017);
- total protein accumulation within the HD filter will be evaluated using appropriate methods;
- coagulation parameters.

Efficiency of HD will be assessed by:

- Blood BUN and potassium levels before and after dialysis;
- length of HD;
- total dialysate urea (measurement of BUN removed over 3 hours of dialysis) will be computed;
    - single pool Kt/V (where Kt = volume of fluid completely cleared of urea [K = dialyzer clearance (mL/min), t=time of dialysis] and V=volume of water a patient's body contains.
    - URR measured as the difference between urea pre-dialysis and post-dialysis expressed as a percentage.

13.6 Dialysate Analysis

A 10 mL dialysate sample will be taken as delineated in the Study Events Flow Chart (Section 6).

The samples will be sent to Aronora and will be stored for up to 5 years following the last dosing for future analysis (e.g., xisomab 3G3 levels and or urea).

Instruction for the sample collection, processing, and sample shipment will be provided separately.

13.7 Pharmacokinetic Assessments

13.7.1 Blood Sampling and Processing

For all patients, blood samples for the determination of free (active) xisomab 3G3 will be collected 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, processing, and sample shipment will be provided separately.

Following completion of the samples analysis, leftover plasma samples will be shipped to the Sponsor, as per their instructions provided separately. Additional analysis for exploratory purposes, including but not limited to factor XI activity, will be performed on leftover plasma samples at the Sponsor's discretion; samples will be stored for up to 5 years following the last dosing for future analysis.

13.7.2 Plasma Pharmacokinetic Parameters

The following PK parameters will be computed, as appropriate, for plasma free xisomab 3G3 from the individual plasma concentrations using a non-compartmental approach:

AUC0-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.
AUC0-inf:	The area under the plasma concentration-time curve from time 0 extrapolated to infinity. AUC0-inf is calculated as the sum of AUC0-t plus the ratio of the last measurable plasma concentration to the elimination rate constant.
AUC%extrap:	Percent of AUC0-inf extrapolated, represented as (1 – AUC0-t/AUC0-inf)*100.
Cmax:	Maximum observed concentration.
Tmax:	Time to reach Cmax. If the maximum value occurs at more than one time point, Tmax is defined as the first time point with this value.

Kel:	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).
t½:	Apparent first-order terminal elimination half-life will be calculated as 0.693/kel.
CL:	Apparent total plasma clearance calculated as Dose/AUC0-inf.
Vss:	Total apparent volume of distribution following single IV dose administration calculated as Vss = MRT x CL. MRT*: Mean residence time = AUMC0-inf/AUC0-inf (for IV infusion) AUCM0-inf*: Area under the moment curve from time 0 to the last measurable concentration, = AUMC0-t + [(tlast x Ct)/ Kel]+ $Ct/(Kel)^2$

* AUMC0-inf and MRT values will be used for Vss calculation but will not be listed in the PK tables.

Additional PK parameters may be computed if deemed appropriate.

Plasma concentrations below the limit of quantitation will be treated as missing for all PK calculations.

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

No value for Kel, t½, AUC0-inf, AUC%extrap, CL, and Vss, as appropriate, will be reported for cases that do not exhibit a terminal log-linear phase in the concentration-time profile.

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

13.7.3 Analytical Method

PK plasma sample analysis will be performed using validated bioanalytical methods.

Samples from patients to be assayed are specified in Section 14.2.

13.8 Blood Volume Drawn for Study Assessments

Table 4: 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 patients only) and serum pregnancy (for female patients only).	1	16	16
On-study hematology and serum chemistry(this includes serum pregnancy for female patients only when scheduled at the same time)	4	12.5	60
On-study coagulation (PT/INR and aPTT)	16	3.5	56
On-study platelet count only **	Up to 14	3.5	Up to 49
On-study BUN and potassium only **	Up to 14	3.5	Up to 49
Blood for PD (aPTT only) **	Up to 17	2.7	Up to 45.9
Blood for PK (free xisomab 3G3)	16	10	160
Blood for Immunogenicity	2	***	***
		Total Blood Volume (mL)→	Up to 435.9 †

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

** Platelet count, BUN and potassium, and aPTT value will be taken from the hematology, serum chemistry, and coagulation sample, respectively, when these are scheduled to be collected at the same time. Samples will not be taken twice at a same timepoint

*** 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 50 mL; this volume could be exceeded only with agreement of the PI on a case-by-case basis).

14 STATISTICAL CONSIDERATIONS

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

14.1 Sample Size Determination

The sample size chosen for this study was selected without statistical considerations. The sample size of up to 24 patients in total (9-12 per cohort with a ratio of 2:1 of active study drug:placebo) has been determined adequate to meet the study safety, tolerability, PD, and PK objectives.

14.2 Population for Analyses

Safety Population: All patients who received the study drug (active or placebo) will be included in the safety evaluations.

PD Population: All patients who received the study drug (active or placebo) and had at least one postdose measurement of any of the PD assessment will be included in the statistical analyses.

PK Population: Samples from all patients receiving the active drug will be assayed even if the patients do not complete the study. All patients receiving the active drug 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.

14.3 Statistical Analyses

Detailed methodology for summary and statistical analyses of the data collected in this study 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.

14.3.1 Safety and Tolerability Analyses

All safety data will be populated in the individual CRFs. All safety data will be listed by patients.

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

Dosing dates and times will be listed by patient.

Incidence and time of bleeding from the HD access sites on the AV fistula (or AV graft), as described in Section 13.2.6, will be counted and recorded. Treatment versus pre-treatment, placebo, and post-treatment results will be compared.

AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA®) available at Celerion and summarized by treatment (2 active dose levels and pooled placebo) for the number of patients reporting the treatment emergent adverse event (TEAE) and the number of TEAEs reported. A by-patient AE data listing including verbatim term, coded term, treatment, severity, and relationship to study drug will be provided.

Safety data including ECGs, vital signs assessments, clinical laboratory results and vascular access site reaction, will be summarized by treatment (2 active dose levels and pooled placebo) and point of time of collection.

Descriptive statistics using appropriate summary statistics will be calculated for quantitative safety data as well as for the difference to baseline, when appropriate. In addition, a shift table describing out of normal range shifts will be provided for clinical laboratory results.

Concomitant medications will be listed by patient and treatment (2 active dose levels and pooled placebo) and coded using the most current version of WHO drug dictionary available at Celerion. Medical history will be listed by patient.

14.3.2 Immunogenicity Analyses

ADA titer will be reported and summarized descriptively.

14.3.3 Pharmacodynamic Analyses

Placebo patients from Cohort 1 and Cohort 2 will be pooled for analysis.

The PD analysis will include assessments of drug potency and efficiency of HD. These will include change in aPTT, BUN, and potassium levels. Change in thrombus accumulation, in total dialysate urea, URR, and Kt/V after xisomab 3G3 levels versus pre-treatment and placebo will also be evaluated. Total protein accumulation within HD filter will be evaluated.

The change from baseline in PD endpoints will be summarized by treatment (2 active dose levels and pooled placebo) and at each scheduled time point using descriptive statistics. The baseline values are any value observed from Day -7 to Day 1, prior to xisomab 3G3 administration. Any values after a single dose of xisomab 3G3 are regarded as post baseline values.

The change from baseline variables will be calculated as the post-baseline value minus the value at baseline.

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

14.3.4 Pharmacokinetic Analyses

Values will be calculated for the plasma concentrations and the PK parameters listed in Section 13.7.2 using appropriate summary statistics to be fully outlined in the SAP.

Pharmacokinetic parameter listings and statistical summaries will be generated separately for each cohort.

Plasma concentration data will also be displayed graphically on the linear and semi-logarithmic scales. Figures will be created to display mean and individual free xisomab 3G3 concentration-time curves, stratified by dose level.

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

15 STUDY ADMINISTRATION

15.1 Ethics

15.1.1 Institutional Review Board

This protocol will be reviewed by the 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 Council on Harmonisation (ICH) guidelines.

15.1.2 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).

15.1.3 Patient Information and Consent

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

Patient will be given a copy of their signed ICF.

15.2 Termination of the Study

Celerion/CRU reserves the right to terminate the study in the interest of patient welfare.

Sponsor reserves the right to suspend or terminate the study at any time.

15.3 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 study is conducted, and that data are generated, documented and reported in compliance with the study protocol, GCP and Good Laboratory Practice 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® or comparable statistical program to check for missing data, data inconsistencies, data ranges, etc. Corrections are made prior to database lock.

15.4 Direct Access to Source Data/Documents

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

Celerion/CRU will ensure that the Sponsor, IRB, and inspection by domestic and foreign regulatory authorities will have direct access to all study-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 study-related monitoring should be done by other parties, they will be required to sign a confidentiality agreement prior to any monitoring and auditing.

15.5 Drug Supplies, Packaging and Labeling

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

The investigational product and matching placebo will be shipped to a designee at the CRU 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 (active and placebo) supplied. At the conclusion of the study, any unused study drugs as well as original containers (even if empty),will be retained by the study site, 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.

15.6 Data Handling and Record Keeping

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

All raw data generated in connection with this study, together with the original copy of the final report, will be retained by CRU 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.

15.7 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).

15.8 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.

15.9 Publication Policy

All unpublished information given to Celerion or the CRU 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.

16 REFERENCES

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