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Protocol Reference Number: ANT-004

NCT Number: NCT04213807

ANTHOS THERAPEUTICS, INC.

MAA868

Clinical Trial Protocol ANT-004

A Multicenter, Randomized, Subject- and Investigator-blinded, Placebo-controlled, Parallel-group, Dose-range Finding Study to Assess the Pharmacokinetic and Pharmacodynamic Parameters, Safety, Tolerability, and Immunogenicity of MAA868 in Patients with Atrial Fibrillation

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Sponsor:	Anthos Therapeutics 55 Cambridge Pkwy, Ste. 103 Cambridge, MA 02142 Tel: 617-430-6940
Chief Medical Officer (CMO)	[redacted]

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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Principal Investigator's Statement and Signature:

I, the undersigned, have read protocol ANT-004 (including all appendices). I agree to conduct the clinical study as described and in compliance with International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements. I agree to inform all who assist me in the conduct of this study of their responsibilities and obligations.

[redacted]

Investigative Site Name, Address and Telephone Number:

[redacted]

Sponsor CMO (or Designee) Approval

Signature:

Name / Title:

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Signature of Principal Investigator **Date**

Name of Principal Investigator (printed)

Investigative Site Name, Address and Telephone Number:

Sponsor CMO (or Designee) Approval

Signature:

Name / Title:

Date:

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Investigative Site Name, Address and Telephone Number:

[redacted]

Sponsor CMO (or Designee) Approval

Signature: [redacted]

Name / Title:

Date:

NOTIFICATION OF SERIOUS ADVERSE EVENTS

Dear Investigator,

You must report a serious adverse event (SAE) (initial or follow-up) to Covance as summarized below. Refer to Section 7.6.2 of the protocol for SAE criteria and additional requirements. See also the Safety Management Plan for further details on the method of reporting a SAE.

- Complete SAE report
- Submit SAE report to Covance safety within 24 hours after awareness of the SAE
- Notify the Covance Medical Lead
- The fax number(s) and email address(es) are located in the Safety Management Plan.

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LIST OF ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
AESI	Adverse event of special interest
AF	Atrial fibrillation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CIAC	central independent adjudication committee
CK	creatine kinase
CI	confidence interval
CRF	case report form
CRNM	clinically relevant non-major
CRO	contract research organization
CSR	clinical study report
DOAC	direct oral anticoagulant
DSS	Drug Safety Services
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
FDA	Food and Drug Administration
FIH	first-in-human
FXI	Factor XI
FXI:C	FXI coagulation activity
GCP	Good Clinical Practice
γGT	gamma glutamyl transferase
GLP	Good Laboratory Practice
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization

IRB	institutional review board
ISTH	International Society of Thrombosis and Haemostasis
IN	investigator notification
MedDRA	Medical Dictionary for Regulatory Activities
PAF	paroxysmal atrial fibrillation
PD	pharmacodynamic
PK	pharmacokinetic
QTcF	QT interval corrected by Fridericia formula
RBC	red blood cells
SAE	serious adverse event
SAP	statistical analysis plan
s.c.	subcutaneous
sCr	serum creatinine
sCT	spiral computed tomography
SD	standard deviation
SOC	system organ class (MedDRA classification)
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
VTE	venous thromboembolism
WBC	white blood cells
WHO	World Health Organization

PHARMACOKINETIC DEFINITIONS AND SYMBOLS

AUC_{0-t}	The area under the plasma concentration-time curve from time zero to time 't' where t is a defined time point after administration [mass x time / volume]
AUC_{inf}	The area under the plasma concentration-time curve from time zero to infinity [mass x time / volume]
AUC_{last}	The area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration [mass x time / volume]
C_0	The initial concentration at the end of an intravenous infusion
CL	The systemic clearance following intravenous administration
C_{max}	The observed maximum plasma concentration following subcutaneous drug administration [mass / volume]
F	Bioavailability
$T_{1/2}$	The terminal elimination half-life [time]
T_{max}	The time to reach the maximum concentration after drug administration [time]
Vss	The steady state volume of distribution following intravenous administration

GLOSSARY OF TERMS

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Dosage	Dose of the study treatment given to the subject in a time unit
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with "investigational new drug" or "test substance"
Screen Failure	A subject who is screened but is not treated or randomized
Subject	A trial participant
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Study treatment period	Interval of time in the planned conduct of a study. A treatment period is associated with a purpose (e.g. screening, randomization, treatment, follow-up), which applies across all arms of a study
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent	Withdrawal of consent from the study is defined as when a subject does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

AMENDMENT #2

Amendment rationale

This protocol is being amended to provide clarification and guidance to sites around changes to the protocol in response to COVID-19 travel restrictions. The sponsor is also using this opportunity to correct inconsistencies and address minor editorial issues.

Changes to the protocol

- Section 2.2 – The primary safety endpoint was clarified to refer to the occurrence of AEs and SAEs which may include clinically significant findings derived from safety assessments such as physical examinations, safety laboratories, assessments of the injection site and others.
- Section 2.3 – Exploratory objective added to include the possibility of assessing the effects of MAA868 on aPTT collected via a point-of-care device.
- Section 3.1 – Language included to enable an earlier assessment of safety in Cohort 1 and in the event the Sponsor and Covance Lead Physician agree there is sufficient data to proceed to Cohort 2 after half of Cohort 1 has been randomized.
- Section 5.6 – Guidance provided in the event of unavoidable study drug interruptions that are unrelated to the study or study drug such as travel-restrictions related to COVID-19 and guidance on study drug resumption.
- Section 7.6 – Further details of the central independent adjudication of bleeding events and major cardiovascular, cerebrovascular, and venous thromboembolic events are provided.
- Section 7.6 – Bleeding event definitions are moved to Appendix 5.
- Section 8.10 – Corrections and clarifications made to how data management and quality control will be handled by the clinical research organization (Covance).

Administrative corrections or clarifications are also made throughout the protocol.

AMENDMENT #1

Amendment Rationale

This protocol is being amended, prior to submission to any Health Authority, to address male contraception requirements, correct inconsistencies and to provide greater clarity.

Changes to the Protocol

- 4.2 (Exclusion criteria) and 6.2 (Study restrictions) – added eligibility criteria and study requirement that male study participants use condoms during intercourse throughout the study.
- 5.4 (Blinding) – added clarity regarding activities for which some associates may have access to the full randomization list prior to database lock in order to fulfill their functions.

PROTOCOL SYNOPSIS

Title of study: A Multicenter, Randomized, Subject- and Investigator-blinded, Placebo-controlled, Parallel-group, Dose-range Finding Study to Assess the Pharmacokinetic and Pharmacodynamic Parameters, Safety, Tolerability, and Immunogenicity of MAA868 in Patients with Atrial Fibrillation

Indication: Atrial fibrillation

Number of Investigators and study centers:

The study is planned to be conducted in approximately 7 sites.

Development phase: Phase 2a

Objectives:

Primary

- To evaluate the proportion of patients that achieve ≥50%, ≥80%, or ≥90% Factor XI (FXI) inhibition at trough after the third dose (Day 91) at different dose levels of MAA868.

Secondary

- To evaluate the proportion of patients achieving FXI inhibition ≥ 50%, ≥80%, and ≥90% at trough after the first and second dose (Day 31 and Day 61) at different dose levels of MAA868.
- To evaluate the safety and tolerability following multiple s.c. administration of MAA868 compared to placebo to patients with AF.
- To evaluate the incidence of major bleeding events, clinically relevant non-major (CRNM) bleeding events and total bleeding with MAA868 relative to placebo during the treatment period.
- To evaluate the immunogenicity of MAA868 compared to placebo.

Study design:

This is a randomized, subject- and investigator-blinded, placebo controlled, dose-ranging study in patients with atrial fibrillation (AF) or atrial flutter who are at low risk for stroke. Patients will be enrolled in up to 3 cohorts of approximately 16 patients each. After a Screening Period of up to 28 days4 weeks, patients in will be randomized in a 3:1 ratio (MAA868:placebo) to receive 3 monthly subcutaneous (s.c.) injections and followed for pharmacokinetics, pharmacodynamic efficacy as well as safety events over the 90-day Treatment Period. Patients will then be followed up to Day 170 during the Washout/Follow-up period.

Number of patients:

Approximately 48 patients will be randomized into the study.

Diagnosis and main criteria for inclusion and exclusion:

Inclusion Criteria

- Male and female patients ≥ 18 and < 85 years old
- Current AF or atrial flutter on 12 lead electrocardiography at Screening
  or
  a history of paroxysmal AF (PAF) or atrial flutter as documented by prior telemetry, 12 lead electrocardiography or ambulatory (e.g. Holter or patch) monitor which is not due to a reversible condition (e.g. alcohol binge drinking)
- A CHA2DS2-VASc risk score of 0-1 for men and 1-2 for women and in whom, in the investigator's judgment, the use of an anticoagulant for stroke prevention is not indicated
- Body weight between 50 and 130 kg, inclusive

Exclusion criteria

- History of stroke, transient ischemic attack or systemic embolism
- History of major bleeding during treatment with an anticoagulant or antiplatelet therapy. (Patients who have had major bleeding on anticoagulants or antiplatelet therapy more than a year ago can be enrolled only if the bleeding was due to a reversible cause, e.g. gastro-duodenal ulcer, that was successfully treated)
- History of traumatic or non-traumatic intracranial, intraspinal or intraocular bleeding.
- Known bleeding diathesis or any known active bleeding at screening or baseline
- Family history of bleeding disorder
- Known active GI lesions predisposing to bleeding events
- Myocardial infarction, unstable angina pectoris or coronary artery bypass graft (CABG) surgery within 12 months prior to the screening period
- Clinically significant moderate or greater mitral stenosis severity (valve area <1.5 cm^2)
- Prosthetic heart valve
- Uncontrolled hypertension defined as SBP/DBP ≥ 160/100 mmHg at the screening visit
- NYHA class III-IV heart failure
- Currently being treated with anticoagulant therapy or have been on anticoagulants in the previous 12 months. Potential patients who have been on anticoagulation more than 12 months ago requires discussion with the sponsor before enrolling.
- Currently being treated with antiplatelet therapy such as a P2Y12 inhibitor or aspirin. Low dose aspirin (≤ 100 mg/d) is allowed
- Severe renal impairment as defined as an estimated glomerular filtration rate ≤45 mL/min/1.73m^2 by the MDRD equation at the screening visit
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception

Test products, dose, and mode of administration:
MAA868 with a dose of 120 mg or 180 mg or placebo s.c. monthly

Reference therapy, dose, dose form, and mode of administration:
Matching placebo to MAA868 s.c. monthly

Duration of patient participation in study:
Planned Screening duration: Up to 28 days
Planned treatment duration: Day 1-91: 90 days
Planned follow-up duration: Day 91 to Day 170: 79 days

Study populations:
Approximately 48 male and female patients age ≥ 18 to < 85 with AF or flutter, as defined above, will be randomized into the study.

Evaluation: Efficacy
- Free FXI concentrations at Days 31, 61 and 91

Evaluation: Safety
- Confirmed major bleeding events, clinically relevant non-major (CRNM) bleeding events and total bleeding events
- Adverse and serious adverse events
- Occurrence of major cardiovascular, cerebrovascular, systemic arterial, and
- Physical examinations
- Monitoring of laboratory parameters in blood
- ECGs
- Hypersensitivity reactions
- Injection site reactions

Evaluation: Other assessments
- Factor XI coagulation activity
- Activated partial thromboplastin time
- Pharmacokinetics
- Development of anti-drug antibodies
- Venous thromboembolic events

Statistical methods:
The patients will be enrolled into cohorts of approximately 16 patients with each cohort evaluating a different dose level of MAA868. Within each cohort, patients will be randomized 3:1 to active drug or placebo.
The primary analysis variable is whether a subject will achieve pre-defined degrees of FXI inhibition at trough (Day 91). The dose regimens and targeted FXI inhibition achievement are as follows:
Low-dose cohort (MAA868 120 mg monthly or placebo): Targeted to achieve ≥ 50% FXI inhibition in 90% of subjects at trough (Day 91).
High dose cohort (MAA868 180 mg monthly or placebo): Targeted to achieve ≥ 90% FXI inhibition in 90% of subjects at trough (Day 91).
The "on treatment" trough FXI levels will be used for the primary analysis, where "on treatment" FXI level is defined as a value which is collected within 30 (±5) days after the last administration of MAA868. The response rate per treatment group will be calculated by number of subjects who achieve targeted FXI inhibition rate divided by the total number of subjects in the treatment group. The estimate of the responder rate (%) at Day 91 will be presented for each dose regimens of MAA868 together with 2-sided 90% confidence intervals.
The secondary efficacy analysis is to evaluate the proportion of subjects achieving FXI inhibition ≥ 50%, ≥80%, and ≥90% at trough after the first and second dose (Day 31 and Day 61) at multiple dose levels of MAA868. The analyses described for the primary endpoint will be repeated for the secondary efficacy variables.
Safety data including adverse events (AEs), bleeding events, ECG, vital signs, thromboembolic events and laboratory results will be reported by count and incidence rate.

1. INTRODUCTION

1.1. Background

AF is the most common cardiac arrhythmia, accounting for approximately one third of hospitalizations for cardiac dysrhythmias. Currently, it is estimated to affect more than 6 million patients in Europe and approximately 2.3 million in the United States, and this number continues to grow rapidly because of the increasing proportion of the aging population with associated co-morbidities. As such, the prevalence of AF is expected to increase 2- to 3-fold over the following 3 decades in western populations (Kannel and Benjamin 2008).

AF is associated with a 4- to 5-fold increase in embolic stroke. The risk for stroke associated with AF increases steeply with age to 23.5% for patients aged 80 to 89 years (Kannel and Benjamin 2008). Most patients with AF require life-long anticoagulation therapy to prevent cardioembolic stroke and systemic embolism. It is estimated that 85 to 90% of AF patients will require anticoagulation therapy (Camm et al 2012).

Vitamin K antagonists (VKA), such as warfarin, are effective in reducing stroke and systemic thromboembolism; a highly significant relative risk reduction in stroke incidence by 67% was observed in a meta-analysis combining six studies (Hart et al 1999). All-cause mortality was reduced (26%) significantly by VKA vs. control (Hart et al 1999). In recent years, direct oral anticoagulant (DOACs) medications have been approved and introduced to clinical practice. These drugs are at least as effective as warfarin in preventing stroke or systemic embolism and may be superior to warfarin in the risk of hemorrhagic stroke and intracranial hemorrhage (Connolly et al 2009, Granger et al 2011, Patel et al 2011). The incidence of major bleeding events with DOACs was similar or slightly lower than the incidence observed with well-conducted warfarin therapy. Nonetheless, the overall bleeding risk continues to be high with the use of DOACs. For instance, the annual incidence of major and clinically relevant non-major (CRNM) bleeding was 14.9% and the annual incidence of major bleeding events was 3.6% in patients treated with rivaroxaban in the ROCKET AF study (Patel et al 2011). It is notable that the occurrence of major bleeding was strongly associated with mortality. In the same study, the rate of all-cause mortality over the 2-month period following a major bleeding event was 20.4% in the rivaroxaban group and 26.1% in the warfarin group (Piccini et al 2014). Thus, there is a high unmet medical need for an anticoagulant therapy that can effectively reduce the risk of AF-related thromboembolic complications such as stroke but with a lower risk of bleeding than currently employed anticoagulants.

FXI is an emerging target for potentially safer and more effective anticoagulant medications. FXI holds important roles in both the intrinsic and extrinsic coagulation pathways and in bridging the initiation and amplification phases of plasmatic hemostasis (Gailani and Renné 2007). Both Factor XII and thrombin can activate FXI, resulting in a sustained thrombin generation and fibrinolysis inhibition. FXI plays a minor role in normal hemostasis in a high tissue factor environment “after vessel injury” whereas it appears to play a key role in thrombosis. Severe FXI deficiency is associated with a lower incidence of ischemic stroke and venous thromboembolic events (Salomon et al 2008, Salomon et al 2011, Preis et al 2017). Nevertheless, bleeding manifestations in subjects with severe FXI deficiency are infrequent and usually mild. Bleeding events that occur are typically injury-related and preferentially affect tissues known to have increased fibrinolytic

activity such as the oral and nasal mucosa, and urinary tract (Bolton-Maggs 2000). Bleeding in vital organs is extremely rare or non-existent.

MAA868

MAA868 is a human antibody that binds to the catalytic domain of FXI. MAA868 binds to both the zymogen (FXI) and activated factor XI (FXIa) with high potency. MAA868 dose-dependently prolonged activated partial thromboplastin time (aPTT) in in-vitro and in-vivo studies. After a single subcutaneous (s.c.) administration of MAA868 at a 3 mg/kg dose, sustained anticoagulant activity lasting for more than one month was observed in cynomolgus monkeys. Moreover, MAA868 prevented experimental carotid artery thrombosis induced by FeCl3 and resulted in a prolongation in aPTT in FXI-/- mice reconstituted with human FXI. No significant toxicity findings were observed in single dose and in the 13-week Good Laboratory Practice (GLP)-compliant toxicity study conducted in cynomolgus monkeys. The highest s.c. dose administered in the 13-week study was defined as no observed adverse effect level NOAEL (100 mg/kg/week s.c.).

MAA868 was evaluated in a first-in-human (FIH) study (CMAA868X2101) to characterize its safety/tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) in healthy subjects following single s.c. administration. In total, 6 cohorts with 10 subjects each (8 MAA868: 2 Placebo) were enrolled. The doses of MAA868 administered in Cohorts 1 to 5 ranged from 5 mg to 240 mg. In a sixth cohort, 240 mg of MAA868 was administered to subjects with body mass index (BMI $\geq$ 35 kg/m2).

In the FIH study, MAA868 appeared to be safe and well tolerated, and the incidence of AEs were comparable across dose groups and placebo. No bleeding events, hypersensitivity reactions or injection site reactions were reported. Exposure increased with increasing dose of s.c. MAA868; the median maximum observed concentration (C_{max}) occurred on Day 7 to 21 and the mean terminal elimination half-life ranged from 20 to 28 days. A dose and time-dependent prolongation of aPTT occurred with MAA868 after single s.c. administration; the 150 mg dose resulted in a mean aPTT prolongation $\geq$ 2-fold at Day 29. Doses greater than 150 mg extended the duration of aPTT prolongation but did not produce a greater prolongation of aPTT. Robust and sustained reductions of free FXI $\geq$ 90% were observed with 150 mg MAA868 at Day 29 and up to Day 43 with 240 mg. A high BMI was associated with a lower MAA868 exposure and slightly shorter duration of aPTT prolongation. Robust reductions in free FXI and in FXI coagulation activity and relevant aPTT prolongation are predicted to occur within 12 to 24 hours after MAA868 s.c. administration with relevant clinical doses.

MAA868 was also studied in healthy Japanese subjects in a single ascending dose, randomized, subject- and investigator-blinded, placebo-controlled, non-confirmatory study to assess safety, tolerability, PK and PD. Three cohorts (MAA868 dose levels: 15, 50 and 150 mg) were enrolled in this study and received a single s.c. dose of MAA868 or matching placebo (8 subjects received MAA868 and 2 subjects received placebo in each cohort). Assessments and assessment schedules were generally similar to the FIH study. No SAE or study discontinuation due to AEs were reported in this study. All AEs were mild in intensity and the distribution of AEs was well balanced between the MAA868 dose groups and placebo. No bleeding event, hypersensitivity or injection site reactions were reported in the study. PK analysis suggested that there was no indication of an impact of the Japanese ethnicity on exposure or PD parameters of MAA868 in healthy subjects.

Taken together, the results from both completed studies of MAA868 suggest that the administration of MAA868 is safe and well-tolerated. Subcutaneous administration of MAA868 leads to robust and sustained effects on aPTT, free FXI, and FXI coagulation activity (FXI:C) up to/through Day 29 with the 150 mg dose and Day 43 with the 240 mg dose in subjects with normal body weight or class 1 obesity (BMI <35 kg/m2). In subjects with class 2 or 3 obesity (BMI ≥35 kg/m2), exposures of MAA868 may be lower and the duration of aPTT prolongation is shorter.

1.2. Study Rationale

This study is a multicenter, randomized, subject and Investigator-blinded, placebo-controlled, parallel-group, multiple ascending dose-ranging study to evaluate the safety, tolerability, PK, and PD effects of MAA868 in patients with AF or flutter at low risk of thromboembolic stroke or peripheral embolism. The trial will evaluate the effects of up to three different doses of MAA868 on FXI inhibition, indices of coagulation, and thrombogenesis biomarkers compared to placebo. The incidence of injection site reactions, bleeding events, immunogenicity, and systemic arterial and venous thromboembolic events will also be assessed. Results from this study will assist with dose-selection of MAA868 for a phase 3 trial in patients with AF.

1.3. Benefit-risk Assessment

AF is associated with a 4- to 5-fold increase in embolic stroke. MAA868, a fully human monoclonal antibody targeting Factor XI, is being considered for development as a novel anticoagulant for patients with AF or flutter. FXI is an emerging target as a novel anticoagulant. Several lines of evidence suggest that FXI inhibition has the potential to prevent thrombosis with minimal risk of bleeding. For example, individuals with an inherited deficiency of FXI have been reported to have a lower risk of VTE even though their bleeding phenotype is variable and often quite mild. Further support of the safety of inhibiting FXI comes from clinical studies using an investigational FXI antisense oligonucleotide (FXI-ASO) where administration of FXI-ASOs in healthy subjects and in patients undergoing total knee arthroplasty was demonstrated to be safe and well-tolerated (Buller et al 2015).

Results from the first-in-human (FIH) study of MAA868 (CMAA868X2101) demonstrated that a single s.c. administration of MAA868 at increasing doses up to 240 mg in healthy subjects were safe and well-tolerated. These doses of MAA868 resulted in a robust and sustained FXI inhibition and prolongation of aPTT. The safety and pharmacodynamic efficacy of MAA868 was further supported by preliminary data from the study CMAA868A1101, which showed a good safety profile of MAA868 in Japanese heathy male subjects.

This study is designed to evaluate the efficacy and safety of achieving different levels of FXI inhibition with different dose levels of s.c. MAA868 in patients with AF or flutter. This study will recruit patients with AF or flutter who are judged by their physician to be at low risk for stroke based on clinical guidelines. In each case, patients will ***only*** be enrolled if their physician has determined that the patient does not merit anticoagulation based on the guidelines and the physician's assessment of the benefit-risk profile for that patient. The guidelines state that the benefits of anticoagulation in AF patients at low risk of embolic stroke are uncertain given the concomitant risks of bleeding with anticoagulant therapy. Accordingly, the guidelines recommend individualized shared physician-patient decision-making with regards to the decision to initiate anticoagulant therapy in this population (January et al 2019). Patients with PAF will be enrolled who have a CHA2DS2-VASc risk score of 0-1 for men or 1-2 for women, in whom the guidelines

are equivocal regarding the recommendation to initiate anticoagulation and advise an individualized assessment of the benefit-risk of anticoagulation (January et al 2019).

Overall, the nonclinical and clinical data to date support the investigation of MAA868 in the prevention of thromboembolic diseases in patients with AF. The risk-benefit relationship appears to be acceptable.

2. OBJECTIVES AND ENDPOINTS

2.1. Primary objective and endpoint

Objective	Endpoint
• To evaluate the proportion of patients that achieve ≥50%, ≥80%, or ≥90% FXI inhibition at trough after the third dose (Day 91) at different dose levels of MAA868	• Occurrence of achieving ≥50%, ≥80%, or ≥90% inhibition of FXI (<50%, <20%, or <10% free FXI) at trough on Day 91 at different dose levels of MAA868

2.2. Secondary objectives and endpoints

Objective	Endpoint
• To evaluate the proportion of patients achieving FXI inhibition ≥50%, ≥80%, and ≥90% at trough after the first and second dose (Day 31 and Day 61) at different dose levels of MAA868	• Occurrence of achieving ≥50%, ≥ 80%, and ≥90% inhibition of FXI (<50%, <20%, or <10% free FXI) at trough on Day 31 and Day 61 at different dose levels of MAA868
• To evaluate the safety and tolerability following multiple s.c. administration of MAA868 compared to placebo in patients with AF	• Occurrence of adverse events (AEs), including serious AEs (SAEs) during the Treatment Period and through EoS
• To evaluate the incidence of major bleeding events, clinically relevant non-major (CRNM) bleeding events and total bleeding with MAA868 relative to placebo during the treatment period	• Occurrence of confirmed major bleeding events, CRNM bleeding events and total bleeding events during the treatment period
• To evaluate the immunogenicity of MAA868 compared to placebo.	• Screening and confirmation for anti-drug (MAA868) antibodies (ADA)

2.3. Exploratory objectives and endpoint

Objective	Endpoint
• To evaluate the effect of MAA868 compared to placebo on the incidence of major cardiovascular, cerebrovascular, and venous thromboembolic events (as defined to the right)	• Occurrence of major cardiovascular, cerebrovascular, systemic arterial, and venous thromboembolic events (VTEs)

• To evaluate the change from baseline in D-dimer and other thrombogenesis markers with MAA868 relative to placebo during the treatment period	• Concentrations of D-dimer and other exploratory thrombogenesis markers during the treatment period
• To evaluate the effect of MAA868 compared to placebo on aPTT as assessed by a point-of-care device	• aPTT measurements collected on a point-of-care device

3. INVESTIGATION PLAN

3.1. Overall Study Design and Plan Description

This is a phase 2a, randomized, subject- and investigator-blinded, placebo-controlled, multiple ascending dose-ranging study to assess the PK/PD, safety, tolerability, and immunogenicity of MAA868 in patients with AF or flutter.

Patients will be enrolled in at least 2 and up to 3 cohorts of approximately 16 patients each for a total of up to 48 subjects (Figure 1A). Patients in cohort 1 will be randomized 3:1 to receive a 120 mg dose of MAA868 or placebo, respectively on Day 1 with two subsequent monthly injections. After approximately 10 of the patients in cohort 1 have been randomized, a safety review of emerging safety and PK data from cohort 1 will take place. Cohort 2 may be initiated after it is confirmed by the Sponsor's Medical Monitor and the Covance Lead Project Physician that the cohort 1 dose was safe and well tolerated after at least half of the patients in cohort 1 have been randomized. Likewise, after approximately 10 of the patients in cohort 2 have received their second dose and have been followed for at least an additional 14 days, interim safety, tolerability, and other analyses will be evaluated by the Sponsor. Based on emerging data, the Sponsor may elect to:

- Enroll cohort 3 to evaluate a higher, lower, or a previously studied dose of MAA868
- Terminate the study

The study is comprised of 3 periods:

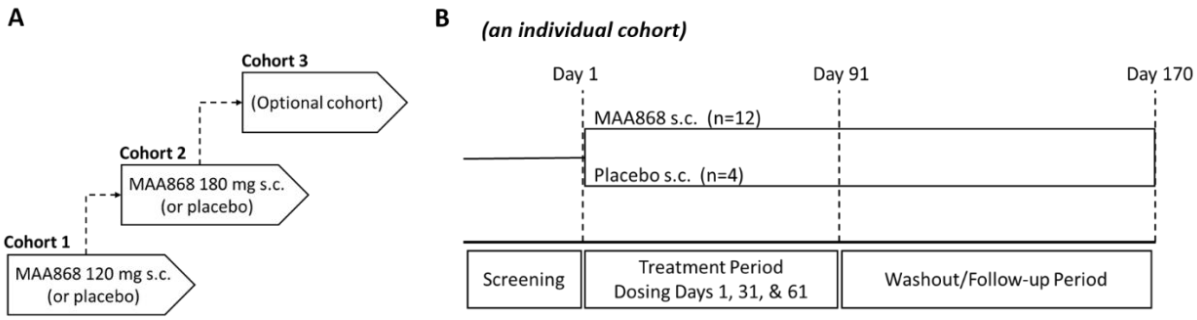
(1) Screening period of up to 28 days

(2) Treatment period with MAA868 administered s.c. monthly (or matching placebo) (randomized 3:1) for 90 days

(3) Follow-up period up to end of study (Day 170).

Following the screening period of up to28 days, all patients that meet the study eligibility criteria (Section 4.1 and Section 4.2) will have baseline efficacy and safety assessments performed on Day 1 and then randomized to active or placebo (Figure 1B).

Figure 1: Overall study design



The first dose of study drug will be administered at the study center on Day 1. The second and third doses of study drug will also be administered at the study center to patients on the Day 31 visit and Day 61 visit, respectively.

During the treatment period, patients will return to the study center on Day 11, Day 31, Day 41, Day 61, Day 71, and Day 91 for safety assessments such as vital signs, AE assessments, laboratory tests, PK, PD, thrombogenesis biomarkers, and other study assessments according to the assessment schedule shown in Table 9.

During the follow-up period, patients will continue to be followed for PK, PD, thrombogenesis, and other study assessments. Patients will return to the study center on Day 101, Day 121 and Day 170 (end of study; EoS) for the evaluations described in the assessment schedule (Table 9).

3.2. Discussion of Study Design, Including the Choice of Control Groups

Rationale for route of administration and treatment duration. The s.c. route of administration was chosen because it is the route of administration anticipated for subsequent studies in patients with AF. In the FIH study of MAA868, the half-life of MAA868 ranged from 20-28 days following s.c. administration. Furthermore, a sustained PD effect of >2-fold mean activated partial thromboplastin time [aPTT] prolongation was observed for ~30 days and returned to the baseline level by ~60 days post-dose after a single 150 mg s.c. dose administration in study X2101. These data support monthly administration of MAA868. Furthermore, assessment of the exposure-response relationship of MAA868 in healthy subjects demonstrated a nearly flat exposure-response for relevant PD parameters (aPTT, FXI coagulation activity and free FXI) at concentrations above 4 µg/mL which is consistent with the Day 29 total MAA868 concentrations achieved with the 150 mg single dose administration in healthy subjects (CMAA868X2101).

Given the half-life of MAA868 and the observed time to return to baseline aPTT levels, a prolonged washout/follow-up period of approximately 110 days from the last dose of MAA868 should be a sufficient monitoring period for patients.

3.3. Selection of Doses in the Study

In the FIH study, single s.c. doses of MAA868 up to 240 mg was safe and well-tolerated. Up to the 150 mg dose, MAA868 produced robust and sustained dose-dependent inhibition of FXI and relevant prolongation of aPTT for approximately 4 weeks. MAA868 doses greater than 150 mg s.c. produced a sustained ~2-fold prolongation of aPTT for greater than 4 weeks.

The precise level of FXI inhibition to achieve a clinically meaningful anticoagulant effect remains unknown. The primary efficacy endpoint of this study will be the number of patients who achieve ≥ 50%, ≥ 80%, or ≥ 90% FXI inhibition [<50%, <20%, or 10% free FXI] at trough on Day 91 following s.c. administration of MAA868. Based on preliminary PK/PD modeling, the doses selected for cohorts 1 and 2 are projected to target the following levels of FXI inhibition:

- Cohort 1 (120 mg dose group). Targeted to achieve ≥ 50% FXI inhibition in 90% of subjects at trough (Day 91).
- Cohort 2 (180 mg dose group). Targeted to achieve ≥ 90% FXI inhibition in 90% of subjects at trough (Day 91).

Based on interim data, an optional cohort 3 may be dosed to add further data to the PK/PD model which will inform dose selection of MAA868 for subsequent studies.

The dosing regimens selected for evaluation in this study are projected to result in exposure (C_{max}) below the C_{max} achieved with a single dose of 240 mg s.c. in healthy subjects in the FIH study.

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

1. Written informed consent must be obtained before any assessment is performed
2. Male and female patients ≥ 18 and < 85 years old with paroxysmal atrial fibrillation (PAF) or atrial flutter on 12 lead electrocardiography at Screening Or
3. Patients with a history of PAF or atrial flutter, as documented by (telemetry, 12 lead electrocardiography or ambulatory [e.g. Holter] monitor) and not due to a reversible condition (e.g. alcohol binge drinking) can be entered even if they do not have PAF at Screening. There is not time-limit for this.
4. Patients with a CHA2DS2-VASc risk score (tool as a predictor for estimating the risk of stroke in patients with AF; Lip et al 2010) of 0-1 for men and 1-2 for women and in whom, in the investigator's judgment, the use of an anticoagulant for stroke prevention is not indicated
5. Body weight between 50 and 130 kg inclusive

4.2. Exclusion Criteria

1. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or until the expected PD effect has returned to baseline, whichever is longer; or longer if required by local regulations.
2. History of stroke, transient ischemic attack or systemic embolism
3. History of major bleeding during treatment with an anticoagulant or antiplatelet therapy. (Patients who have had major bleeding on anticoagulants or antiplatelet therapy more than a year ago can be enrolled only if the bleeding was due to a reversible cause, e.g. gastro-duodenal ulcer that was successfully treated.)
4. History of traumatic or non-traumatic intracranial, intraspinal or intraocular bleeding
5. Known bleeding diathesis or any known active bleeding site at screening or baseline
6. Family history of bleeding disorder
7. Known active GI lesions predisposing to bleeding events
8. Myocardial infarction, unstable angina pectoris or coronary artery bypass graft (CABG) surgery within 12 months prior to the Screening period
9. Known clinically significant valvular heart disease including moderate or severe mitral stenosis (valve area <1.5 cm^2).
10. Patients with a prosthetic heart valve
11. Uncontrolled hypertension defined as SBP/DBP ≥ 160/100 mmHg at the Screening visit
12. Patients with NYHA Class III- IV heart failure
13. Currently being treated with anticoagulant therapy or have been on anticoagulants in the previous 12 months. Potential patients who have been on anticoagulation more than 12 months ago requires discussion with the sponsor before enrolling.
14. Treatment with antiplatelet therapy such as either a P2Y12 inhibitor or aspirin. (Low dose aspirin ≤ 100 mg/d) is allowed.)
15. Severe renal impairment as defined as an estimated glomerular filtration rate ≤45 mL/min/1.73m^2 by the MDRD equation at the Screening Visit

16. Positive test for human immunodeficiency virus (HIV), positive hepatitis B (hepatitis B surface antigen [HBsAg]) or hepatitis C (anti-hepatitis C antibody [Anti-HCV]) at Screening
17. Significant illness, per Investigator judgement, which has not resolved within four (4) weeks prior to dosing
18. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during their time in the study. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment
    - Male sterilization of sexual partner (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
    - Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception

    In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.
    Women are considered post-menopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment with FSH is she considered not of child-bearing potential.
    Male subjects must also agree to use highly effective methods of contraception during their time in the study and should not father a child or donate sperm in this period.
19. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
20. Patients with either a psychiatric disease or substance abuse history, which in the opinion of the Investigator could interfere with protocol compliance.
21. Any surgical or medical condition, which in the opinion of the Investigator, may place the patient at higher risk from his/her participation in the study, or is likely to prevent the patient from complying with the requirements of the study or completing the study.

4.3. Discontinuation Criteria

Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Patients who do not meet the criteria for participation in this study may be rescreened; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis.

Withdrawal of informed consent

Subjects may voluntarily withdraw from the study for any reason at any time.

Withdrawal from the study can occur when a subject chooses to do one or more of the following:

- Does not want to participate in the study anymore
- Does not want any further visits or assessments
- Does not want any further study-related contacts
- Does not allow analysis of already obtained biologic material.

If a subject who has received one or more doses of the study drug determines that they no longer want to participate the Investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason(s) for the subject's decision to withdraw his/her consent, record this information and conduct any assessments and visits still allowed.

In the event the subject withdraws consent prior to beginning dosing, the study treatment will not be administered. The data that would have been collected at subsequent visits will be considered missing. Further attempts to contact the subject are allowed when safety findings require follow-up.

Lost to Follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the Investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject cannot be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

4.4. Stopping Rules

Overall study stopping rules:

Enrollment in the study will be placed on hold if the Sponsor considers that the number and/or severity of AEs, abnormal safety monitoring tests or abnormal laboratory findings justify putting the study on hold.

The study may resume following the safety review, if the Investigator and Sponsor's Medical Monitor agree it is safe to proceed.

5. STUDY TREATMENTS

5.1. Treatments Administered

MAA868 drug product is a sterile, preservative-free liquid in vial for subcutaneous (s.c.) or intravenous (i.v.) administration. Each drug product vial contains 150 mg of MAA868 active ingredient per 1 mL plus 20% (0.2 mL) overfill which allows for complete withdrawal of the labeled dose (150 mg). [redacted] The excipients utilized are standard pharmacopoeial excipients that are commonly used in parenteral products. MAA868 will be provided as a 150 mg/mL solution in 6 mL single-use vials (with 1.2 mL fill). The 180 mg dose will require 2 vials. 0.8 and 1.2 mL should be withdrawn into a syringe and administered subcutaneously for the 120 mg and 180 mg doses, respectively.

Table 1: Overview of Study Medication

Study Treatment Name:	MAA868	Placebo
Dosage Formulation:	Liquid (in vial)	Liquid (in vial)
Unit Dose Strength(s)/Dosage Level(s):	150 mg/mL	Placebo to MAA868
Route of Administration:	SC injection	SC injection
Packaging and Labeling:	Study Treatment will be provided in vials. Each vial will be labeled as required per country requirement.	Placebo will be provided in vials. Each vial will be labeled as required per country requirement.
Provided by:	Anthos	Anthos

5.2. Preparation, Storage, Handling, and Accountability

Details on the requirements for storage and management of study treatment, and instructions to be followed for subject numbering, prescribing/dispensing and administering study treatment are outlined in the Pharmacy Manual.

MAA868 drug product vials should be stored refrigerated at 2°- 8°C and protected from light. A disposable syringe will be used to administer the s.c. injection.

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment. Only patients enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study treatment are provided in the Pharmacy Manual.

5.3. Method of Treatment Assignment

Subjects in each cohort will be randomized to MAA868 or placebo in a ratio of 12: 4 as follows.

- Cohort 1 = 120 mg MAA868 monthly s.c. or placebo
- Cohort 2 = 180 mg MAA868 monthly s.c. or placebo
- Cohort 3 (if necessary) = TBD mg MAA868 monthly s.c. or placebo

Randomization numbers will be assigned in ascending, sequential order to eligible subjects. The Investigator will enter the randomization number on the CRF.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A randomization list will be produced by or under the responsibility of Covance statistician using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio. The randomization scheme for subjects will be reviewed and approved by a member of the Covance Randomization Group.

Patients will be replaced at the Sponsor's discretion. Replacement subjects will be assigned randomization numbers 6101-6316 If a subject requires a replacement, the replacement subject will be assigned a randomization number corresponding to the original subject (e.g., Subject 6103 would replace Subject 1103).

The table below provides the general details of the numbering of the subjects for randomization:

Table 2: Randomization Assignment Numbering

Cohort	Randomization numbers	Replacement randomization numbers
I	1101-1116	6101-6116
II	1201-1216	6201-6216
III	1301-1316	6301-6316

5.4. Blinding

This is a subject- and investigator-blinded study. Subjects will remain blinded to study treatment throughout the study, except where indicated below.

The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

Site staff

With the exception of any unblinded pharmacist or pharmacy designee, all site staff (including study investigator and study nurse(s)) will be blinded to study treatment during treatment allocation and subject dosing. Appropriate measures must be taken by any unblinded pharmacist or pharmacy designee to ensure that the treatment assignments are concealed from the rest of the site staff.

Unblinding a single subject at the site for safety reasons (necessary for subject management) will occur via an emergency system in place at the site (see Section 5.10).

Site staff may also be unblinded to the treatment assignment of one or more subjects (within a single cohort or across cohorts as necessary), or an entire cohort at the initial cohort safety

evaluation timepoint if deemed appropriate to aid decision-making. The decision to un-blind site staff will be determined by the clinical trial team based on need or review of the entire study group will be performed at a pre-selected time.

Sponsor staff

The following unblinded Sponsor roles (or designee) are required for this study:

- Field monitor(s) (evaluation of drug dispensing and reconciliation)
- Physician not directly involved in study conduct
- Sample analyst(s) (PK blood)
- Study statistician
- Programmers and other personnel involved in study data analysis

An unblinded Covance Physician not directly involved in study conduct may receive a copy of the randomization schedule (via request to the Randomization Office), to facilitate analysis of aPTT safety labs that would otherwise unblind study Investigators. The unblinded Medical Monitor will alert the Investigator and Sponsor of any safety concerns.

The sample analysts will receive a copy of the randomization schedule (via request to the Randomization Office), to facilitate analysis of the samples. The sample analysts will provide the sample data to the study team under blinded conditions unless otherwise allowed.

The study statistician will be able to access the full randomization list from the start of the study and is allowed to share unblinded information with the rest of the clinical trial team as appropriate for internal decision purposes. For example, unblinded summaries and unblinded individual data can be shared with the team whenever necessary.

Study programmers and other personnel involved in study data analysis (e.g. biomarker expert, pharmacometrician, modeler(s)) are allowed to access treatment assignment information from the start of the study for the purpose of data analysis.

The clinical trial team is allowed to share unblinded results with other Sponsor staff (e.g. decision boards) as required for internal decision making on the study or the project while the study is ongoing.

All unblinded personnel will otherwise keep randomization lists and data or information that could un-blind other study team members confidential and secure except as described above.

Following final database lock all roles may be considered unblinded.

5.5. Treating the subject

MAA868 will be administered to the subject by study staff via s.c. administration. See the Pharmacy Manual for further details.

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

5.6. Permitted dose adjustments and interruptions of study treatment

Dosing interruptions are permitted in the case of logistical reasons not related to study therapy, e.g., an unrelated event such as a COVID-19-related travel restriction or any other restriction or safety concern with the subject traveling to the study site. The reason for interruption should be documented in the patient's study record.

Once the restriction(s) leading to study drug interruption have been lifted and the Sponsor and Investigator agree that it is safe for the subject to resume study participation, the subject may be resumed on study therapy on a case-by-case basis upon discussion with the Sponsor. Subjects who received only 1 dose of study drug before interruption may either resume study drug with the second dose or may restart with the first dose of study drug if a sufficient amount of time has elapsed such that the expected PD effect has returned to baseline.

5.7. Study Completion and Post-study Treatment

Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them.

Study completion is defined as when the last subject completes their EoS visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

All subjects will be required to attend the EoS visit and have related assessments collected as per the Schedule of assessments (Table 9). All SAEs reported during this time period must be reported as described in Section 7.6.2. and the Safety Management Plan. Documentation of attempts to contact the subject should be recorded in the source documentation.

5.8. Discontinuation of Study Treatment

The Investigator may decide to suspend the s.c. administration of the study drug if symptoms or signs consistent with an injection site reaction or hypersensitivity reaction occur.

Subjects who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 4.3, Withdraw of Informed Consent). Where possible, they should return for the EoS assessments indicated in the assessment table. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in Section 4.3 (Lost to follow-up). This contact should preferably be done according to the study visit schedule.

5.9. Study Termination

The study can be terminated by Anthos at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. Should this be necessary, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject and followed until the aPTT has returned to baseline. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The Investigator will be responsible for informing the Institutional Review Board (IRB) of the early termination of the trial.

5.10. Emergency breaking of assigned treatment code

Emergency unblinding must only be undertaken when it is essential to treat the subject safely and efficaciously, such as in the event of clinically significant bleeding events. Most often, knowledge of the possible treatment assignments is sufficient to treat a study subject who presents with an emergency condition. A complete set of emergency code break cards will be provided to the Investigator site(s) and a complete set will be available at Anthos and Covance. All code break cards must be retained until the end of the study and retained by the site as a source document. They must be stored in a secure place but be accessible to the Investigator 24 hours per day in case of emergency. The Investigator will receive a blinded code break card for each subject. In an emergency, the code break may be opened to determine the treatment. There is no known reversal agent for MAA868 (see Section 6.2).

The code break should not be opened for any reason other than an emergency. If the Investigator opened the code break, he/she must note the date, time, and reason for removing it and retain this information with the case report form documentation. The unblinded treatment code must not be recorded on the CRF. The Investigator must also immediately inform the study monitor that the code has been broken.

It is the Investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the code break cards at any time in case of emergency. The Investigator will need to provide:

- Protocol number
- Study drug name (if available)
- Subject number.

In addition, the Investigator must provide oral and written information to inform the subject how to contact his/her backup in cases of emergency when he/she is unavailable to ensure that un blinding can be performed at any time.

6. CONCOMITANT THERAPIES

6.1. Concomitant therapy

The Investigator must instruct the subject to notify the study staff of any new medications (including nutritional supplements and herbal medications) that he/she takes after being enrolled into the study.

All prescription medications, OTC drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the Investigator should contact Covance before randomizing a subject or, if the subject is already enrolled, to determine if the subject should continue participation in the study.

During the study, in the event the Investigator elects to start the patient on chronic antithrombotic therapy, anticoagulation or antiplatelet therapy should not be started until the patient's aPTT has returned to baseline.

Reporting medication errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient/subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

All study treatment errors and uses outside of what is foreseen in the protocol will be collected in the Dose Administration Record CRF. Study treatment errors are only to be reported to Covance DSS department if the treatment error is associated with an SAE.

All instances of misuse or abuse must be documented in the AE CRF irrespective of the misuse/abuse being associated with an AE/SAE. In addition, all instances of misuse or abuse must be reported to the Covance DSS department. As such, instances of misuse or abuse are also to be reported using the SAE form/CRF. Table 3 summarizes the reporting requirements.

Table 3: Summary of reporting requirements for medication errors

Treatment error type	Document in Dose Administration CRF	Document in AE CRF	Complete SAE form/CRF
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see Section 7.6.1 and Section 7.6.2, respectively.

6.2. Study restrictions

Pregnancy and contraception

Women of child-bearing potential are not permitted to participate in this study, unless they agree to use highly effective methods of contraception during their time in the study.

During their time in the study, sexually active male subjects must agree to use highly effective methods of contraception and should not father a child or donate sperm in this period.

Prohibited treatment

Use of the following medications is not allowed during the course of the study from screening (Visit 1) through the EoS. Patients who are receiving such medication(s) will be excluded, or if ethically and clinically justified, the medication(s) should be gradually withdrawn at least seven days before the baseline visit:

- Use of chronic antiplatelet agents such as clopidogrel or ticagrelor is prohibited; however, use of low-dose aspirin (≤100 mg per day) is permitted.
- Use of chronic systemic anticoagulants such as warfarin, low molecular weight heparin or heparinoids, or direct oral anticoagulants such as apixaban or dabigatran. Patients may be started on chronic anticoagulation during the Washout/Follow-up period once their aPTT has returned to baseline, at the Investigator's discretion.
- Use of any therapeutic monoclonal antibody regardless of the indication during the study.

Dietary restrictions

- No alcohol for 48 hours before each clinic visit (from Screening through the EoS visit). During the study, alcohol consumption will be restricted to no more than 2 drinks/day for males and 1 drink/day for females.
- Patients should not make significant alterations in their diet (e.g., going on weight loss diet) while in the study.
- During the study, caffeinated beverages will be restricted to no more than 3 cups/day.

Other restrictions

No strenuous physical exercise or activities which have an increased risk of injury or falling should be undertaken until after the EoS visit.

6.3. Reversal medication

There is currently no specific antidote for MAA868. FXI concentrates (not marketed in the US) are unlikely to be effective as the excess in free MAA868 concentrations in the circulation is expected to quickly neutralize the exogenous FXI.

Recombinant FVIIa can bypass the hypocoagulopathy and restore hemostasis in patients with severe FXI deficiency. Administration of intermediate to high doses of rFVIIa (40 to 90 µg/kg) resulted in supra-physiological levels of FVII and thromboembolic complications in patients with severe FXI deficiency (Riddell et al 2011). Low doses of rFVIIa are associated with lower prothrombotic risk. Riddell et al reported their experience in 4 patients with severe FXI deficiency undergoing surgery (Riddell et al 2011); patients were administered rFVIIa 30 µg/kg and tranexamic acid 1 g i.v. at induction of anesthesia. Subsequent bolus doses of rFVIIa 15–30 µg/kg were administered at 2 to 4 hourly intervals as guided by rotational thromboelastometry for 24 48 hours and tranexamic acid 1 g every 6 hourly for 5 days. Low doses of rFVIIa and tranexamic acid were safe and effective in restoring hemostasis in severe FXI deficiency in this study. In another study comprising 4 patients with severe FXI deficiency with inhibitor who experienced 5 surgeries (Livnat et al 2009), 1 g of tranexamic acid was given 2 hours before surgery, immediately prior to the interventions then every 6 hour for at least 7 days; moreover, rFVIIa was administered at doses ranging from 15 to 30 µg/kg at the completion of surgery. This protocol secured normal hemostasis in patients with severe FXI deficiency with inhibitor.

Based on the above, rFVIIa can be recommended as a preferred therapeutic option to restore hemostasis in subjects with active, non-accessible bleeding site and in subjects requiring immediate reversal of the MAA868 PD effects prior to an urgent surgery. Please see the Investigator's Brochure - Summary of the data and guidance for the investigator for a more complete discussion.

7. STUDY ASSESSMENTS AND PROCEDURES

7.1. Assessment schedule

Subjects should be seen for all visits/assessments as outlined in the assessment schedule (Table 9).

Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the study treatment discontinuation (TD) visit will be performed.

7.2. Informed consent procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB-approved informed consent.

The Sponsor, or Sponsor designee, will provide to investigators a proposed informed consent form that complies with the ICHE6 Good Clinical Practice (GCP) guideline and regulatory requirements and is considered appropriate for this study. The informed consent form will also include a section related to optional future research which will require a separate consent checkbox if the subject agrees to future research. Any changes to the proposed consent form suggested by the Investigator must be agreed to by the Sponsor before submission to the IRB.

Information about common side effects already known about the investigational drug can be found in the IB. This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and then must be discussed with the subject.

Ensure subjects are informed of the contraception requirements outlined in the Section 4.2 (Exclusion criteria).

A copy of the approved version of all consent forms must be provided to the Covance monitor after IRB approval.

7.3 Subject screening

In general, it is permissible to re-screen a subject if s/he fails the initial Screening or falls out of the screening window timelines; however, each case must be discussed and agreed with the Sponsor Medical Monitor on a case-by-case basis. A new screening number will be assigned to a subject who is re screened, thus no screening number will be used twice.

Reasons for screen failure will be documented in the site log.

7.4 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data will be collected on all subjects. Relevant medical history/current medical conditions data will also be collected until signature of informed consent.

Investigators have the discretion to record abnormal test findings on the medical history CRF, if in their judgment, the test abnormality occurred prior to the informed consent signature.

Hepatitis screen, HIV screen

All subjects will be screened for HIV, Hepatitis B and C.

Alcohol test and drug screening

All subjects will be screened for alcohol and substances of abuse.

7.5 Efficacy Assessments

The PD samples will be collected at the timepoints defined in the Assessment schedule (Table 9). Follow instructions outlined in the Central Laboratory Manual regarding sample collection, numbering, processing and shipment.

In order to better define the PD profile, the timing of the sample collection may be altered based on emergent data. The number of samples/blood draws and total blood volume collected will not exceed those stated in the Laboratory Manual.

PD samples will be obtained and evaluated in all subjects at all dose levels.

7.5.1 Free FXI

Free FXI concentrations (FXI that is not bound to MAA868) will be measured in plasma. A detailed description of the assay methods will be included in the Bioanalytical Data Report.

7.5.2 aPTT

aPTT, calibrated for FXI deficiency, and aPTT using a standard laboratory protocol and/or point of care device will be measured at all timepoints indicated in the Assessment schedule (Table 9).

aPTT will be determined in plasma. The detailed method descriptions of the assay will be included in the Bioanalytical Data Report.

7.5.3 Total FXI

Total FXI concentrations (FXI that is either bound to MAA868 or free) will be measured in plasma. A detailed description of the assay methods will be included in the Bioanalytical Data Report.

7.5.4 FXI coagulation activity (FXI:C)

FXI:C will be measured in plasma. A detailed description of the assay methods will be included in the Bioanalytical Data Report.

7.6 Safety Assessments

Safety assessments are specified below; assessments will be collected as specified in the Assessment Schedule (Table 9).

Bleeding

All suspected bleeding events will be documented by the Investigator in the appropriate CRF. All documentation regarding suspected bleeding events will be forwarded for adjudication. The central

independent adjudication committee (CIAC) will classify the bleeding events as major bleeding, CRNM bleeding, nuisance bleeding, or no bleeding. For definition of major bleeding the criteria of the International Society of Thrombosis and Haemostasis (ISTH) for non-surgical patients (Schulman et al 2005) is referred to. Further definitions can be found in the CIAC charter.

The members of the CIAC will be blinded to treatment assignment. Further details and procedures surrounding adjudication of bleeding events are in the CIAC charter.

The population is those who have received at least one dose of the study drug.

Major cardiovascular, cerebrovascular, and venous thromboembolic events

All suspected major cardiovascular, cerebrovascular, and VTE events will be documented by the Investigator in the appropriate CRF including any diagnostic imaging that was used to confirm the event. For instance, any suspected episodes of DVT (i.e., swelling, localized pain, redness, heat, localized warmth) must be documented by compression ultrasound (CUS) or venography.

Any suspected episodes of PE (i.e., shortness of breath, chest pain, coughing, tachycardia, hemoptysis, hemodynamic compromise, unexplained death) must be documented by ventilation/perfusion lung scintigraphy, spiral computed tomography (sCT), or pulmonary angiography.

All major cardiovascular, cerebrovascular, systemic arterial, and venous thromboembolic events (VTEs) including deaths for which a major cardiovascular, cerebrovascular, or VTE event could not be ruled out will be adjudicated by experienced medical personnel that is blinded to treatment assignment.

The adjudicated outcome will be the basis for any interim and final safety evaluations.

7.6.1 Adverse Events

An AE is any untoward medical occurrence [i.e., any unfavorable and unintended sign (including abnormal laboratory findings), symptom or disease] in a subject or clinical investigation subject after providing written informed consent for participation in the study until the EoS visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the study treatment are also considered an AE irrespective if a clinical event has occurred. See Section 7.6.2 for an overview of the reporting requirements.

The occurrence of AEs must be sought by non-directive questioning of the subject at each visit during the study. AEs also may be detected when they are volunteered by the subject during or between visits or through physical examination finding, laboratory test finding, or other assessments.

Abnormal laboratory values or test results constitute AEs only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in healthy subjects. Investigators have the responsibility for managing the safety of individual subject and identifying AEs. Alert ranges for liver and kidney related events are included in Appendix 1 and Appendix 2, respectively. Additional clinically notable laboratory values are included in Appendix 3.

AEs must be recorded on the AE CRF under the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

1. Severity grade

- mild: usually transient in nature and generally not interfering with normal activities
- moderate: sufficiently discomforting to interfere with normal activities
- severe: prevents normal activities

2. Relationship to the study treatment

- Related
- Possibly related
- Not related

3. Duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.

4. Whether it constitutes a SAE (see Section 7.6.2 for definition of SAE) and which seriousness criteria have been met

5. Action taken regarding investigational treatment.

All AEs must be treated appropriately. Treatment may include one or more of the following:

- no action taken (e.g. further observation only)
- concomitant medication or non-drug therapy given
- hospitalization/prolonged hospitalization (see Section 7.6.2 for definition of SAE)

6. Outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown).

Information about common side effects already known about the investigational drug can be found in the IB. Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the investigational drug, the interventions required to treat it, and the outcome.

The Investigator must also instruct each subject to report any new AE (beyond the protocol observation period) that the subject, or the subject's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the Investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Covance.

7.6.2 Reporting Serious Adverse Events

Definition of SAE

An SAE is defined as any AE [appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s)] which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - elective or pre-planned treatment for a pre-existing condition and has not worsened since the start of study drug
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - social reasons and respite care in the absence of any deterioration in the subject's general condition
    - is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (see Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (see Annex IV, ICH-E2D Guideline).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All AEs (serious and non-serious) are captured on the CRF; SAEs also require individual reporting to Covance Drug Safety & Epidemiology (DS&E).

SAE Reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last planned study assessment, must be reported to Covance within 24 hours of learning of its occurrence as described below. Any SAEs

experienced after this period should only be reported to Covance if the Investigator suspects a causal relationship to study treatment.

Note: SAEs reported by subjects deemed to be screen failures must be reported to Covance as outlined here with appropriate information also captured in the CRFs.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the Investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Follow- up information provided must describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable) and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the IB (new occurrence) and is thought to be related to the study treatment a Covance DS&E associate may urgently require further information from the Investigator for Health Authority reporting. Covance may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Follow the detailed instructions outlined in the Safety Management Plan regarding the submission process for reporting SAEs to Covance. Note: SAEs must be reported to Covance within 24 hours of the Investigator learning of its occurrence/receiving follow-up information.

7.7 Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events must be followed.

Please refer to Appendix 1 for complete definitions of liver events.

Follow-up of liver events

Every liver event defined in Appendix 1 should be followed up by the Investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 4 of Appendix 1.

- Repeating liver chemistry tests (ALT, AST, total bilirubin (TBL), PT/INR, ALP and γGT) to confirm elevation as soon as possible

  These liver chemistry repeats should always be performed using the central laboratory, with the results provided via the standard electronic transfer. If results are needed quickly then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously

conducted that are associated with this event should be available to Covance and the Sponsor.

- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to Section 4.3 (Discontinuation of study treatment), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
    - Repeating liver chemistry tests two or three times weekly. Testing should include ALT, AST, ALP, PT/INR, and γGT. If total bilirubin is elevated > 2 x ULN, fractionation into direct and indirect bilirubin is required. To rule out muscular origin of transaminase elevations, CPK should be measured along with liver chemistry tests. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic. Retesting should be continued up to resolution.
    - Obtaining a more detailed history of symptoms and prior or concurrent diseases.
    - Obtaining a history of concomitant drug use (including non-prescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
    - Exclusion of underlying liver disease, as specified in Table 6.
    - Imaging such as abdominal US, CT or MRI, as appropriate
    - Obtaining a history of exposure to environmental chemical agents.
    - Considering gastroenterology or hepatology consultations.

All follow up information, and the procedures performed must be recorded as appropriate in the CRF.

7.8 Renal safety monitoring

Renal laboratory alerts and renal events must be followed up by the Investigator or designated personnel at the trial site. Recommended follow-up assessments are listed in Appendix 2.

7.9 Pregnancy

All female study participants, regardless of the requirement to be of non-child-bearing potential to be enrolled into this study, will have pregnancy testing. See the Assessment Schedule (Table 9), for timing of the protocol required pregnancy testing; additional pregnancy testing may be performed to meet local requirements*. Subjects will not receive study medication in case of a positive urine or serum pregnancy test.

*If additional pregnancy testing is needed per local requirements, those additional results will be kept as source documentation only.

Pregnancy reporting

Reproductive toxicity and teratogenicity data are not available for this antibody at this time, therefore no guidelines on therapeutic recommendations in case of pregnancy are available. This study enrolls women who are considered to be of non-child-bearing potential, thus pregnancy is not an expected outcome for any female study participant. However, in the case that a pregnancy in a female study participant should occur please follow the below reporting guidelines. The follow-up for this subject and for the fetus is at the discretion of the Investigator.

To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Covance within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the Investigator to the local Covance DSS department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

All assessments that are considered as a risk during pregnancy must not be performed. The subject may continue all other protocol assessments.

7.10 Clinical Laboratory Evaluations

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Covance personnel. The results should be evaluated for criteria defining an AE and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Covance personnel should be contacted.

Safety labs (hematology, clinical chemistry and urinalysis) do not need to be repeated at baseline if the Baseline visit is taking place within 48 hours of the screening labs being collected from an individual subject.

Subjects should be instructed to fast for at least 8 hours prior to scheduled safety lab collections.

Clinically notable laboratory findings are defined in Appendix 3.

Hematology

Hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differentials and platelet count will be measured.

Clinical chemistry

Sodium, potassium, creatinine, BUN/urea, uric acid, chloride, albumin, calcium, alkaline phosphatase, total bilirubin, bicarbonate/HCO_3, LDH, GGT, AST, ALT, CK, glucose, total

cholesterol, triglycerides. If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

Urinalysis

Measurements for specific gravity, protein, glucose and blood will be performed. Microscopy, WBC, RBC and sediments will also be assessed in case of an abnormal test result.

Special clinical laboratory evaluations

Stool samples will be collected to check for occult blood at screening and baseline. Screening fecal samples can be collected at any time during the Screening period, and baseline fecal samples must be collected within 72 hours of Day 1. If fecal screening samples are collected within 72 hours of Day 1, then they do not need to be repeated for the Baseline visit. In the event that a subject is unable to produce a stool sample for sampling, the site medical staff may elect to produce a sample via digital extraction from the rectum.

Details regarding collection methods and processing are outlined in the Central Laboratory Manual.

7.11 Vital Signs, Physical Examination, and Other Safety Evaluations

Vital signs will include the collection of oral body temperature (recorded in °C), blood pressure (BP)–sitting and standing –and pulse measurements. At Screening, for eligibility determination, three sets of systolic and diastolic BP and pulse rate measurements will be collected after the subject has been sitting for 3 minutes, with back supported and both feet placed on the floor and the mean will be used to determine eligibility. A single set of BP and pulse rate measurements will then be collected after three minutes in the standing position.

A single set of sitting BP measurements will be collected at subsequent visits.

Physical exams will include assessment of general appearance, skin, lymph nodes, HEENT, neck, thorax/lungs, cardiovascular, abdomen, musculoskeletal, and neurological systems.

Height in centimeters (cm) and body weight [to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes] will be measured. Body mass index (BMI) will be calculated using the following formula:

BMI = Body weight (kg) / [Height (m)]$_2$. BMI results will be documented in the CRF to 2 decimal places.

7.12 Electrocardiogram (ECG)

The ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. PR interval, QRS duration, heart rate, RR interval, QT, QT corrected by the Fridericia correction formula (QTcF) will be collected. The QTcF should be used for clinical decision-making. ECGs must be collected, analyzed and appropriately signed and archived at the study site; the site will also store all ECG readings digitally (if possible). For any ECGs with subject safety concerns, duplicate ECGs must be performed to confirm the safety finding. Clinically significant ECG findings at baseline must be discussed with the Sponsor before administration of study treatment. Clinically significant abnormalities must be reported in the AE CRF.

7.13Pharmacokinetic Analysis

The PK samples will be collected at the timepoints defined in the Assessment schedule (Table 9). Follow instructions outlined in the Central Laboratory Manual regarding sample collection, numbering, processing and shipment. See Section 7.15 regarding the potential use of residual samples.

In order to better define the PK profile, the timing of the PK sample collection may be altered based on emergent data. The number of samples/blood draws and total blood volume collected will not exceed those stated in the Laboratory Manual. Changes to the PK Assessment schedule, if any, will be communicated to the sites in the dose adjustment minutes.

The PK samples will be obtained and evaluated in all subjects at all dose levels. Untreated (placebo) samples will not be analyzed.

Concentrations of plasma total MAA868 (i.e. MAA868 that is bound to FXI or not bound to FXI) will be determined by a validated LC-MS/MS method. A detailed description of the method used to quantify the concentration of total MAA868 will be included in the bioanalytical raw data and in the Bioanalytical Data Report.

All concentrations below the LLOQ or missing data will be labeled as such in the concentration data listings.

For standard PK abbreviations and definitions see the list provided at the beginning of this protocol.

The following PK parameters will be determined, where data permit, using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.2 or higher): C_0 (the concentration at the end of infusion), AUC_{last}, AUC_{inf}, C0/D, and AUC/D, based on the plasma concentration data.

The linear trapezoidal rule will be used for AUC calculation. The terminal half-life of MAA868 ($T_{1/2}$), volume of distribution (V_{ss}) and clearance (C_L) will also be estimated, if feasible, based on the data.

7.14 Other assessments

7.14.1 Exploratory Biomarker assessments

Biomarkers including, but not limited to, D-Dimer and biomarkers of thrombogenesis and coagulation may also be studied.

The list may be changed or expanded further, as it is recognized that more relevant or novel biomarkers may be discovered during the conduct of the study.

Sample(s) will be collected at the timepoint(s) defined in the Assessment schedule (Table 9).

Follow instructions for sample collection, numbering, processing and shipment provided in the central lab manual. Detailed descriptions of the assays will be included in the Bioanalytical Data Reports.

7.14.2 Immunogenicity (IG)

The IG samples will be collected at the timepoints defined in the Assessment schedule (Table 9).

Follow instructions outlined in the Central Laboratory Manual regarding sample collection, numbering, processing, and shipment. See Section 7.15egarding the potential use of residual samples.

Immunogenicity analytical method(s)

A ligand-binding assay will be used to detect anti-MAA868 antibodies. The analytical method will be described in detail in the IG Bioanalytical Data Report.

7.15 Use of residual biological samples

Residual blood samples may be used for another protocol specified endpoint.

Any residual samples remaining after the protocol-defined analysis has been performed may be used for additional exploratory analysis. This may include but is not limited to using residual samples for protein binding, metabolite profiling, biomarkers of transporters or metabolic enzyme activity (such as 4-beta-hydroxycholesterol levels) or other bioanalytical purposes (e.g. cross check between different sites and/or stability assessment). Given the exploratory nature of the work, the analytical method used for those assessments may not be validated. As such, the results from this exploratory analysis will not be included in the clinical study report.

8. SAMPLE SIZE AND DATA ANALYSES

8.1. Determination of Sample Size

A sample size of 16 subjects per treatment dose cohort with a ratio of 3:1 for MAA868 and placebo treatment assignment is based on historic data considerations. For example, if the observed proportion of patients in a cohort achieving target levels of inhibition is 11/12, the 90% confidence interval would be 0.66 to 0.996.

8.2. Analysis Populations

All Randomized Set will include all subjects who are randomized

Full Analysis Set will include randomized subjects excluding those subjects who are randomized into the study in error and did not receive study drug. Subjects will be analyzed based on the assigned treatment at the randomization.

Per Protocol Set will include subjects in Full Analysis Set and those subjects have no major protocol deviation after randomization.

Safety Set will include randomized subjects who at least received one dose of study drug. Subjects will be analyzed based on the actual treatment taken.

PK/PD Analysis Set will comprise all subjects who received at least one dose of study drug and have at least one PK/PD assessment. Subjects will be analyzed based on the actual treatment taken.

8.3. General Considerations

All efficacy analysis will be based on the Full Analysis Set or Per Protocol Set and will be performed based on the assigned treatment arm at the randomization. Only descriptive statistics will be summarized, no statistical inference will be calculated in efficacy.

Safety analysis will be performed using Safety Set. Subjects will be analyzed based on the actual treatment taken.

PK and PD analysis will be based on PK/PD Analysis Set.

Continuous variables will be summarized by number of subjects [n], mean, standard deviation [SD], median, minimum [min], and maximum [max]. Categorical variable will be summarized using frequency [N] and percentage [%].

8.4. Demographics and Baseline characteristics

All baseline summaries will be based on the All Randomized Set and Full Analysis Set populations.

Gender, race and ethnicity will be summarized using counts and percentages. Age, height (cm), and weight (kg) will be summarized with descriptive statistics (number of subjects [n], mean, SD, median, minimum [min], and maximum [max]). Age may be summarized by decades using N and %.

The listing of subjects with abnormal physical examination findings at screening will be presented. The number and percent of subjects with medical history events will be summarized. Vital signs

collected at screening (sitting diastolic and systolic blood pressure, pulse, temperature and body weight) will be summarized with descriptive statistics (n, mean, SD, median, min, and max).

8.5. Efficacy Analysis

Primary Efficacy Outcome Measures

Within each treatment cohort patients will be randomized 3:1 to active drug or placebo.

The primary analysis variable is whether a subject will achieve a certain percentage FXI inhibition at trough (Day 91). The response rate per treatment group will be calculated by number of subjects who achieve targeted FXI inhibition rate divided by the total number of subjects in the treatment group. The dose regimens and targeted FXI inhibition achievement for Cohorts 1 and 2 are as follows

Cohort 1 (MAA868 120 mg monthly or placebo): Targeted to achieve ≥ 50% FXI inhibition in 90% of subjects at trough (Day 91).

Cohort 2 (MAA868 180 mg monthly or placebo): Targeted to achieve ≥ 90% FXI inhibition in 90% of subjects at trough (Day 91).

The "on treatment" trough FXI levels will be used for the primary analysis, where "on treatment" FXI level is defined as a value which is collected within 30 (±5) days after the last administration of MAA868. The estimate of the responder rate (%) at Day 91 will be presented for each dose regimens of MAA868 together with 2-sided 90% confidence intervals (CI) computed via the Clopper-Pearson exact binomial method.

Secondary Efficacy Outcome Measures

The secondary efficacy analysis is to evaluate the proportion of subjects achieving FXI inhibition ≥ 50%, ≥80%, and ≥90% at trough after the first and second dose (Day 31 and Day 61) at 3 dose levels of MAA868. The analyses described for the primary endpoint will be repeated for the secondary efficacy variables as follows:

- Cohort 1 (MAA868 120 mg monthly or placebo): at Day 31 and 61.
- Cohort 2 (MAA868 180 mg monthly or placebo): at Day 31 and 61
- Cohort 3 (MAA868 TBD mg monthly or placebo): at Day 31 and 61

8.6. Safety Analysis

The safety evaluation includes the analysis of bleeding events, AEs, major cardiovascular, cerebrovascular, systemic arterial, and venous thromboembolism events, laboratory data, ECG, vital signs, hypersensitivity reactions, injection site reactions, and development of anti-drug antibodies. All safety analysis will be performed using the Safety Set.

Adverse Events

The Investigator's verbatim term of each AE will be mapped to system organ class (SOC) and preferred term (PT) using the MedDRA dictionary.

Treatment-emergent Adverse Events (TEAEs) will be of primary interest. The TEAEs will be summarized by SOC and PT; a subject will only be counted once per SOC and once per PT within a treatment. If a subject reports more than one AE with the same PT, the AE with the maximum severity will be presented. Subject counts and percentages and event counts will be presented for each treatment and totaled for all treatments for the following summaries:

- All TEAEs
- Serious TEAEs
- All TEAEs by severity
- All TEAEs by relationship to study drug
- TEAEs potentially related to study drug
- TEAEs potentially related to study drug by severity
- TEAEs leading to discontinuation of study drug
- TEAEs leading to withdrawal from the study

Adverse events of special interest (AESI) will be reported for a selection of interested AE terms that are specific to Sponsor's product and program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor can be appropriate.

The AESIs for this study are defined as follows:

1. TERM 1
2. TERM 2

Similarly, to the TEAE summary, the AESI will be summarized in the following:

1. All AESIs
2. Serious AESIs
3. All AESIs by severity
4. All AESIs by relationship to study drug
5. AESIs leading to discontinuation of study drug
6. AESIs leading to withdrawal from the study

No statistical inference between the treatments will be performed on AEs.

Listings will be presented by subject for all TEAEs, AESIs, as well as for SAEs, TEAEs associated with outcome of death, and TEAEs leading to discontinuation from the study.

Bleeding Events

An analysis will be performed for the composite safety endpoint of major and CRNM bleeding events which occur on-treatment from the first dose of the study drug to the last dose of the study drug + 30 days if the subject permanently discontinues the study drug prior to the third dose on Day 91. The number of events and the incidence of adjudicated bleeding events will be tabulated

based on ISTH definition by treatment including the composite endpoint of major bleeding events and/or CRNM bleedings.

Major bleeding events (Yes/No)

CRNM bleeding events (Yes/No)

Total bleeding events (Yes/No)

If a subject has more than one bleeding event in each above category, the subject will be counted only once in the tabulation.

The adjudicated outcome by the CIAC will be the basis for any interim and final analysis.

Major cardiovascular, cerebrovascular, and venous thromboembolic events

An analysis will be performed for the composite safety endpoint of major cardiovascular, cerebrovascular, and venous thromboembolic events which occur on-treatment from the first dose of the study drug to the last dose of the study drug + 30 days if the subject permanently discontinues the study drug prior to the third dose on Day 91.

The number of events and the incidence of adjudicated events will be tabulated based on the outcomes adjudicated by experienced medical personnel, and the adjudicated outcome will be the basis for any interim and final analysis.

Clinical Laboratory Evaluations

Clinical laboratory results in continuous values at each timepoint and for change from baseline will be displayed using summary statistics (n, mean, median, SD, minimum and maximum values).

A laboratory value that is within the central laboratory's reference range will be considered normal. A laboratory value that is outside the central laboratory's normal range will be considered abnormal and will be flagged as either high (H) or low (L). The number and percentage of subjects with abnormal laboratory values will be summarized for each scheduled visit. In addition, shift tables will be presented to display the shift in the normal range categories (L, normal [N], H) from baseline to specified timepoint. Laboratory results in clinical significance will also be summarized in tabulation.

All clinical laboratory data will be presented in listings. Baseline is defined as the result obtained prior to first administration of study medication. Laboratory data will be summarized in SI units.

Vital Sign Measurements

Pre-dose values, post-dose values, and the change from baseline in vital sign measurements (sitting diastolic and systolic blood pressure, pulse, temperature and body weight) will be summarized with descriptive statistics (n, mean, SD, median, min, and max) at each timepoint by treatment. The baseline value will be value just prior to first administration of study medication.

ECG Parameters

The ECG measures (QTc-F, QT, RR, ventricular rate, PR, and QRS) will be listed and summarized with descriptive statistics (n, mean, SD, median, min, and max) at each timepoint by treatment.

The listings of subjects with abnormal ECG results, as judged by the Investigator, will be displayed and will be calculated. The baseline will be the value just prior to first administration of study medication.

8.7. Pharmacokinetic Analysis

Descriptive summary statistics will be provided by treatment and visit/sampling timepoint with descriptive statistics (n, mean, SD, median, min, and max) at each timepoint by treatment. An exception to this is T_{max} where median, minimum and maximum will be presented.

Concentrations below the lower limit of quantitation (LLOQ) will be treated as zero in summary statistics and for PK parameter calculations. A geometric mean will not be reported if the dataset includes zero values.

Individual total MAA868 plasma concentration data will be listed by treatment (MAA868 arms only), subject, and visit/sampling timepoint. PK parameters will also be listed by treatment and subject.

8.8. Biomarkers

Coagulation parameters, including free and total FXI, FXI:C, and immunogenicity will be summarized by timepoint and treatment.

8.9. Interim Analysis (IA)

Safety and tolerability data (AEs, laboratory assessments, vital signs and ECG data) will be evaluated from Cohort 1 by the Sponsor's Medical Monitor and Covance Lead Project Physician after approximately 10 of the patients in cohort 1 have received their second dose of study drug and have been followed for at least an additional 14 days. The decision to proceed to cohort 2 will be made only after it is confirmed that the cohort 1 dose was safe and well tolerated. and the Sponsor determines there is adequate data to proceed to cohort 2. If notable AEs or safety concerns are found in cohort 1, the study may be terminated.

Likewise, after approximately 10 of the patients in cohort 2 have received their second dose of study drug and have been followed for at least an additional 14 days, safety, tolerability, and other analyses will be evaluated.

Additional IAs may be conducted to support decision making at any time concerning the current clinical study, the Sponsor’s clinical development projects in general or in case of any emergent safety concerns. The Investigator(s) may be included for decisions with regards to any unplanned IAs that address questions of subject safety.

Unblinded IA results will be reviewed by the Sponsor (or their designees).

No further dissemination of interim results should occur, in particular not with individuals involved in treating the study’s subjects or assessing clinical data (e.g. ECGs, symptoms) obtained in the study.

8.10. Data Quality Assurance

Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Covance representative will review the protocol and CRFs with the Investigator(s) and their staff. During the study Covance employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The monitor will visit the site to check the completeness of subject records, the accuracy of entries on the CRFs, the adherence to the protocol and to GCP, the progress of enrollment, and ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits.

The Investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The Investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Covance monitoring standards require full verification for the presence of informed consent, adherence to the eligibility criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

Data collection

Designated Investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the electronic data capture (EDC) system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to Covance working on behalf of Anthos. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the Investigator will receive copies of the subject data for archiving at the investigational site.

Data not requiring a separate written record are noted on the Assessment schedule (Table 9) and can be recorded directly on the CRF. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

Database management and quality control

Covance will review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. System queries are sent to the investigational site using an electronic data query which will appear in eCRF once data have been entered and saved. Manual queries will be raised by Data Management in eCRF based ongoing manual review. Designated investigator site staff is required to respond to the query in the eCRF and confirm or correct the data.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally, and the results will be sent electronically to Covance.

At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Covance.

The occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked, and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Anthos Head of Regulatory and the Chief Medical Officer.

9. ETHICAL CONSIDERATIONS

9.1. Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

9.2. Responsibilities of the Investigator and IRB

Before initiating a trial, the Investigator/institution must obtain approval/favorable opinion from the IRB for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Covance monitors, auditors, Covance Quality Assurance representatives, designated agents of Anthos, IRBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the Investigator must inform Anthos immediately that this request has been made.

For multi-center trials, a Coordinating Investigator will be selected by Anthos around the time of Last Patient Last Visit to be a reviewer and signatory for the CSR.

9.3. Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. Upon study completion and finalization of the study report the results of this trial will be posted in a publicly accessible database of clinical trial results in accordance with local regulations.

No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement between the Sponsor and the investigator and/or the investigator's institution.

The information developed from this clinical study will be used by the Sponsor in connection with the development of MAA868 and other drugs and diagnostics, and thus may be disclosed as required to other clinical investigators, business partners, or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the Sponsor with all data obtained in the study.

10. PROTOCOL ADHERENCE

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances is an Investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an Investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Anthos and approved by the IRB and health authorities, where required, it cannot be implemented.

10.1. Protocol Amendments

Any change to the protocol can only be made in a written protocol amendment that must be approved by Anthos, Health Authorities where required, and the IRB prior to implementation.

Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB is notified.

Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7.6.2 (Safety Monitoring) must be followed and the Study Lead informed.

11. REFERENCES

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12. APPENDICES

12.1. Appendix 1 - Liver Event Definitions and Follow-up Requirements

Table 4: Liver Event and Liver-Related Laboratory Alert Definition

Definition	Thresholds
Potential Hy's law cases	• ALT or AST > 3 X ULN and TBL > 2 × ULN without initial increase in ALP to > 2 × ULN
ALT or AST elevation with coagulopathy	• ALT or AST > 3 × ULN and INR > 1.5 (in the absence of anticoagulation)
ALT or AST elevation accompanied by symptoms	• ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash, or eosinophilia
Isolated ALT or AST elevation	• ALT or AST > 8 × ULN • 5 x ULN < ALT/AST ≤ 8 x ULN • 3 x ULN ALT/AST 5 x ULN
Isolated ALP elevation	• ALP > 2 × ULN (in the absence of known bone pathology)
Others	• Any clinical event of jaundice (or equivalent term) Any adverse event potentially indicative of liver toxicity

Table 5: Action required for Liver Events and Liver-Related Laboratory Alerts

Criteria	Action required
Potential Hy's law cases ALT or AST elevation with coagulopathy ALT or AST elevation accompanied by symptoms Isolated ALT or AST elevation > 8 X ULN Jaundice	• Hospitalize, if clinically appropriate • Establish causality • Complete CRFs per liver event guidance
Isolated ALT or AST elevation > 5 to ≤ 8 X ULN	• Establish causality • Complete CRFs per liver event guidance
Isolated ALT or AST elevation > 3 to ≤ 5 × ULN (patient is asymptomatic)	• Monitor liver chemistry tests two or three times weekly
Isolated ALP elevation	• Repeat liver chemistry tests within 48-72 hours • If elevation is confirmed, measure fractionated ALP; if >50% is of liver origin, establish hepatic causality • Complete CRFs per liver event guidance
Any AE potentially indicative of liver toxicity	• Hospitalize if clinically appropriate • Complete CRFs per liver event guidance

Table 6: Exclusion of underlying Liver Disease

Disease	Assessment
Hepatitis A, B, C, E	• IgM anti-HAV; HBSAg, IgM anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	• ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	• Ethanol history, γGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	• Ultrasound or MRI
Hypoxic/ischemic hepatopathy	• Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI
Biliary tract disease	• Ultrasound or MRI, ERCP as appropriate
Wilson disease	• Caeruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-anitrypsin

12.2. Appendix 2 - Specific Renal Alert Criteria and Actions

Table 7: Specific Renal Alert Criteria and Actions

Criteria	Action required
Serum creatinine (sCr) increase 25 – 49% compared to baseline	• Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase ≥ 50%	• Consider causes and possible interventions • Repeat assessment within 24-48 hours if possible • Consider hospitalization and specialized treatment
Protein-creatinine or albumin-creatinine ratio increase ≥ 2-fold, or new onset proteinuria ≥ 1+ , or Albumin-creatinine ratio (ACR) ≥ 30 mg/g or ≥ 3 mg/mmol, or Protein-creatinine ratio (PCR) ≥ 150 mg/g or >15 mg/mmol	• Consider causes and possible interventions • Assess serum albumin and serum protein • Repeat assessment to confirm
New onset glucosuria on urine exam (unless related to concomitant treatment, diabetes)	<u>Assess and document:</u> • Blood glucose (fasting) • Serum creatinine • Urine albumin-creatinine ratio
New hematuria on urine exam	<u>Assess and document</u> • Urine sediment microscopy • Assess sCr and urine albumin-creatinine ratio • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

Additional specialized assessments are available to assess renal function or renal pathology.
(Note: In exceptional cases when a nephrologist considers a renal biopsy, it is strongly recommended to make specimen slides available for evaluation by Anthos to potentially identify project-wide patterns of nephrotoxicity.)
Whenever a renal event is identified, a detailed subject history and examination are indicated to identify, document and potentially eliminate risk factors that may have initiated or contributed to the event:

- Blood pressure assessment (after 5 min rest, with an appropriate cuff size)
- Signs and symptoms such as fever, headache, shortness of breath, back or abdominal pain, dysuria, hematuria, dependent or periorbital edema
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output
- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other potential causes of renal dysfunction, e.g., dehydration, hemorrhage, tumor lysis

Table 8: Follow-up renal events

Action	Follow up
Assess*, document and record in the CRF or via electronic data load. Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc.) in the CRF	• Urine exam and sediment microscopy • Blood pressure and body weight • Serum creatinine, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate, and uric acid • Urine output
Monitor subject regularly (frequency at Investigator's discretion) until:	• Event resolution: (sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline) OR • Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.

*Urine osmolality: in the absence of diuretics or chronic kidney disease this can be a very sensitive metric for integrated kidney function that requires excellent tubular function. A high urinary osmolality in the setting of an increase in sCr will point toward a "pre-renal" cause rather than tubular toxicity.

12.3. Appendix 3 - Clinical notable laboratory values

Clinical notable laboratory values:

The definition, the specific alert criteria and the corresponding actions for hepatic and renal notable laboratory abnormalities are respectively provided in Appendix 1 and Appendix 2.

The following laboratory values are considered clinically notable and should be forwarded to Covance at the same time that they are sent to Investigators:

- A change from baseline in hemoglobin ≥ 2 g/dL
- A decrease from baseline in platelets count ≥ 50% or < 100 x 10^9/L
- A positive fecal occult blood test
- Macroscopic hematuria

Whenever a clinically notable laboratory value is identified, a detailed subject history and examination are indicated to identify, document and potentially eliminate a bleeding event:

- Blood pressure assessment (after 5 min rest, with an appropriate cuff size);
- Signs and symptoms such as shortness of breath, tiredness, abdominal pain, hematemesis, rectorrhagia, melena, gingival or nose bleeding, bruising and hematoma;
- Concomitant events or procedures such as trauma, surgical procedures.

When one of the above occurs the action plan is as follows:

- Confirm the value, assess and document the clinically notable laboratory value in the CRF or via electronic data load;
- Investigate the underlying causes such as clinical or subclinical bleeding event and the contributing factors such as intake of prohibited medications;
- Monitor subject regularly (frequency at Investigator's discretion) until resolution or stabilization. Hospital admission, additional laboratory tests, endoscopy, volume replacement, transfusion, etc. should be performed at the Investigator's discretion and according to the medical needs (see Section 6.3 for reversal therapy).

12.4. Appendix 4 - Schedule of Assessments

Table 9: Schedule of Assessments

Period	Screening	Treatment							Washout / Follow-up			
Visit	1	2	3	4	5	6	7	8	9	10	TD	EoS
Day	-28 to -3	1 (predose)	11	31 (predose)	41	61 (predose)	71	91	101	121	-	170
Window			±2	±2	±3	±2	±3	±2	±3	±3		±10
Informed consent	X											
Medical history	X											
Drug & alcohol screen	X											
I/E criteria	X	X										
Physical Exam	X	X	X	X		X		X		X	X	X
Height	X											
Weight	X	X										X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X						X				X
HIV, Hepatitis B, Hepatitis C	X											
aPTT, Free and total FXI	X	X	X	X	X	X	X	X	X	X	X	X
aPTT (corrected for FXI), FXI:C		X				X		X				X
PK assessment: total MAA868		X	X	X	X	X	X	X	X	X		X
Antidrug antibodies (ADA)		X		X		X	X	X		X		X
Exploratory biomarker collection	X	X		X		X		X		X		
Complete safety Labs	X	X	X	X	X	X		X		X	X	X
Pregnancy test	Serum	Urine			Urine			Urine			Urine	Urine
Urine	X	X	X	X	X	X		X		X	X	X
Fecal occult blood test	X	X										
AE collection	X											
Concomitant meds	X											
Local assessment of CV and cerebrovascular events		X										
Local assessment of bleeding events		X										
Dispense Study Medications		X		X		X						
Drug Accountability		X		X		X		X				
MAA868		X		X		X						
Placebo		X		X		X						

Period	Screening	Treatment							Washout / Follow-up			
Visit	1	2	3	4	5	6	7	8	9	10	TD	EoS
Day	-28 to -3	1 (predose)	11	31 (predose)	41	61 (predose)	71	91	101	121	-	170
Window			±2	±2	±3	±2	±3	±2	±3	±3		±10
Injection site inspection (post-dose)		X	X	X	X	X	X					
Study disposition								X			X	X
TD = Study treatment discontinuation; EoS = End of Study; FXI:C = Factor XI coagulation activity												

12.5. Appendix 5 – Definition of bleeding events

Major bleeding event:

A major bleeding event will be confirmed when it is a clinically overt bleeding event that meets at least one of the following:

a) Fatal bleeding

b) Bleeding in a critical area or organ such as:

- Retroperitoneal
- Intracranial
  - Intracranial bleeding will be further classified as either
    - Subdural
    - Epidural
    - Subarachnoidal
    - Intra-cerebral
    - Undetermined.
- Intraocular
- Intraspinal
- Intra-articular
- Pericardial
- Intramuscular with compartment syndrome

c) A clinically overt bleeding event

- that is associated with a fall in hemoglobin of 2.0 g/dL (>1.24 mMol/L) or more, or
- leading to a transfusion of ≥ 2 units of packed red blood cells or whole blood.

Note: The (temporal) relationship of the hemoglobin drop (and or the need for transfusion) with the overt bleeding will be carefully evaluated since a gradual decrease of hemoglobin and need for transfusions may occur without direct association with an overt bleeding and then would not lead to classification major. In the case of surgical procedure related bleeding, the bleeding must be in excess of that normally associated with the surgery/procedure.

Clinically relevant non-major bleeding event

A bleeding event will be classified as a clinically relevant non-major (CRNM) bleeding event if it is overt not meeting the criteria for major bleeding, requires medical attention or is associated with discomfort for the subject such as pain, or impairment of activities of daily life. Examples of bleeding requiring medical attention include, but are not limited to, bleeding events that result in the following diagnostic or therapeutic measures:

- Requires or prolongs hospitalization;

- Diagnostic tests: laboratory evaluations, imaging studies, endoscopy, colonoscopy, cystoscopy, or bronchoscopy;
- Therapeutic intervention such as: nasal packing, ultrasound guided closure of an aneurysm, coil embolization, surgery.

Clinical examples that might classify as CRNM:

- Intramuscular hematoma or subcutaneous (skin) hematoma if the size is larger than 25 cm2, or 100 cm2 if provoked, or
- epistaxis (profuse) lasting longer than 5 minutes, if it is repetitive (i.e. 2 or more episodes of true bleeding, i.e. not spots on a handkerchief, within 24 hours), or lead to an intervention (packing, electrocoagulation etc.), or
- hematuria if it is macroscopic, and either spontaneous or lasts for more than 24 hours after instrumentation (e.g. catheter placement or surgery) of the urogenital tract, or
- macroscopic gastro-intestinal hemorrhage: at least one episode of melena/hematemesis, if clinically apparent, or rectal blood loss, if more than a few spots on toilet paper, or
- hemoptysis, if more than a few speckles in the sputum and not occurring within the context of PE

Nuisance (not clinically relevant) bleeding events

Other overt bleeding events that do not fulfill the criteria of a major bleeding event or a clinically relevant non-major bleeding event will be classified as a nuisance bleeding event.

Note: All other suspected bleeding events (e.g., decline in hemoglobin with no overt bleeding) will be classified as “no bleeding event.”

ANTHOS THERAPEUTICS, INC.

MAA868

Clinical Trial Protocol ANT-004

A Multicenter, Randomized, Subject- and Investigator-blinded, Placebo-controlled, Parallel-group, Dose-range Finding Study to Assess the Pharmacokinetic and Pharmacodynamic Parameters, Safety, Tolerability, and Immunogenicity of MAA868 in Patients with Atrial Fibrillation

Document type:	Protocol
IND number:	129008
EUDRACT number:	N/A
Version number:	V02 - Amendment 1
Clinical Trial Phase:	IIa
Release date:	1-November-2019
Sponsor:	Anthos Therapeutics 55 Cambridge Pkwy, Ste. 103 Cambridge, MA 02142 Tel: 617-430-6940
Chief Medical Officer (CMO)	[redacted]

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Protocol Number: ANT-004

Protocol Title: A Multicenter, Randomized, Subject- and Investigator-blinded, Placebo-controlled, Parallel group, Dose-range Finding Study to Assess the Pharmacokinetic and Pharmacodynamic Parameters, Safety, Tolerability, and Immunogenicity of MAA868 in Patients with Atrial Fibrillation

Principal Investigator's Statement and Signature:

I, the undersigned, have read protocol ANT-004 (including all appendices). I agree to conduct the clinical study as described and in compliance with International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements. I agree to inform all who assist me in the conduct of this study of their responsibilities and obligations.

[redacted]

Name of Principal Investigator (printed)

Investigative Site Name, Address and Telephone Number:

[redacted]

Sponsor CMO (or Designee) Approval

Signature:

Name / Title:

Date:

[redacted]

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Protocol Number: ANT-004

Protocol Title: A Multicenter, Randomized, Subject- and Investigator-blinded, Placebo-controlled, Parallel group, Dose-range Finding Study to Assess the Pharmacokinetic and Pharmacodynamic Parameters, Safety, Tolerability, and Immunogenicity of MAA868 in Patients with Atrial Fibrillation

Principal Investigator's Statement and Signature:

I, the undersigned, have read protocol ANT-004 (including all appendices). I agree to conduct the clinical study as described and in compliance with International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements. I agree to inform all who assist me in the conduct of this study of their responsibilities and obligations.

Signature of Principal Investigator **Date**

[redacted]
Name of Principal Investigator (printed)

Investigative Site Name, Address and Telephone Number:

[redacted]

Sponsor CMO (or Designee) Approval

Signature:

Name / Title:

Date:

[redacted]

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Protocol Number: ANT-004

Protocol Title: A Multicenter, Randomized, Subject- and Investigator-blinded, Placebo-controlled, Parallel group, Dose-range Finding Study to Assess the Pharmacokinetic and Pharmacodynamic Parameters, Safety, Tolerability, and Immunogenicity of MAA868 in Patients with Atrial Fibrillation

Principal Investigator's Statement and Signature:

I, the undersigned, have read protocol ANT-004 (including all appendices). I agree to conduct the clinical study as described and in compliance with International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements. I agree to inform all who assist me in the conduct of this study of their responsibilities and obligations.

[redacted]

Name of Principal Investigator (printed)

Investigative Site Name, Address and Telephone Number:

[redacted]

Sponsor CMO (or Designee) Approval

Signature:

Name / Title:

Date:

[redacted]

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Protocol Number: ANT-004

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[redacted]

Name of Principal Investigator (printed)

Investigative Site Name, Address and Telephone Number:

[redacted]

Sponsor CMO (or Designee) Approval

Signature: [redacted]

Name / Title:

Date:

NOTIFICATION OF SERIOUS ADVERSE EVENTS

Dear Investigator,

You must report a serious adverse event (SAE) (initial or follow-up) to Covance as summarized below. Refer to Section 7.6.2 of the protocol for SAE criteria and additional requirements. See also the Safety Management Plan for further details on the method of reporting a SAE.

- Complete SAE report
- Submit SAE report to Covance safety within 24 hours after awareness of the SAE
- Notify the Covance Medical Lead
- The fax number(s) and email address(es) are located in the Safety Management Plan.

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LIST OF ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
AESI	Adverse event of special interest
AF	Atrial fibrillation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CK	creatine kinase
CI	confidence interval
CRF	case report form
CRNM	clinically relevant non-major
CRO	contract research organization
CSR	clinical study report
DOAC	direct oral anticoagulant
DSS	Drug Safety Services
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
FDA	Food and Drug Administration
FIH	first-in-human
FXI	Factor XI
FXI:C	FXI coagulation activity
GCP	Good Clinical Practice
γGT	gamma glutamyl transferase
GLP	Good Laboratory Practice
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
IRB	institutional review board

IN	investigator notification
MedDRA	Medical Dictionary for Regulatory Activities
PAF	paroxysmal atrial fibrillation
PD	pharmacodynamic
PK	pharmacokinetic
QTcF	QT interval corrected by Fridericia formula
RBC	red blood cells
SAE	serious adverse event
SAP	statistical analysis plan
s.c.	subcutaneous
sCr	serum creatinine
sCT	spiral computed tomography
SD	standard deviation
SOC	system organ class (MedDRA classification)
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
VTE	venous thromboembolism
WBC	white blood cells

PHARMACOKINETIC DEFINITIONS AND SYMBOLS

AUC_{0-t}	The area under the plasma concentration-time curve from time zero to time 't' where t is a defined time point after administration [mass x time / volume]
AUC_{inf}	The area under the plasma concentration-time curve from time zero to infinity [mass x time / volume]
AUC_{last}	The area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration [mass x time / volume]
C_0	The initial concentration at the end of an intravenous infusion
CL	The systemic clearance following intravenous administration
C_{max}	The observed maximum plasma concentration following subcutaneous drug administration [mass / volume]
F	Bioavailability
$T_{1/2}$	The terminal elimination half-life [time]
T_{max}	The time to reach the maximum concentration after drug administration [time]
Vss	The steady state volume of distribution following intravenous administration

GLOSSARY OF TERMS

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Dosage	Dose of the study treatment given to the subject in a time unit
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with "investigational new drug" or "test substance"
Screen Failure	A subject who is screened but is not treated or randomized
Subject	A trial participant
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Study treatment period	Interval of time in the planned conduct of a study. A treatment period is associated with a purpose (e.g. screening, randomization, treatment, follow-up), which applies across all arms of a study
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent	Withdrawal of consent from the study is defined as when a subject does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

AMENDMENT #1

Amendment Rationale

This protocol is being amended, prior to submission to any Health Authority, to address male contraception requirements, correct inconsistencies and to provide greater clarity.

Changes to the Protocol

- 4.2 (Exclusion criteria) and 6.2 (Study restrictions) – added eligibility criteria and study requirement that male study participants use condoms during intercourse throughout the study.
- 5.4 (Blinding) – added clarity regarding activities for which some associates may have access to the full randomization list prior to database lock in order to fulfill their functions.

PROTOCOL SYNOPSIS

Title of study: A Multicenter, Randomized, Subject- and Investigator-blinded, Placebo-controlled, Parallel-group, Dose-range Finding Study to Assess the Pharmacokinetic and Pharmacodynamic Parameters, Safety, Tolerability, and Immunogenicity of MAA868 in Patients with Atrial Fibrillation

Indication: Atrial fibrillation

Number of Investigators and study centers:

The study is planned to be conducted in approximately 6 sites.

Development phase: Phase 2a

Objectives:

Primary

- To evaluate the proportion of patients that achieve ≥50%, ≥80%, or ≥90% Factor XI (FXI) inhibition at trough after the third dose (Day 91) at different dose levels of MAA868.

Secondary

- To evaluate the proportion of patients achieving FXI inhibition ≥ 50%, ≥80%, and ≥90% at trough after the first and second dose (Day 31 and Day 61) at different dose levels of MAA868.
- To evaluate the safety and tolerability following multiple s.c. administration of MAA868 compared to placebo to patients with AF.
- To evaluate the incidence of major bleeding events, clinically relevant non-major (CRNM) bleeding events and total bleeding with MAA868 relative to placebo during the treatment period.
- To evaluate the immunogenicity of MAA868 compared to placebo.

Study design:

This is a randomized, subject- and investigator-blinded, placebo controlled, dose-ranging study in patients with atrial fibrillation (AF) or atrial flutter who are at low risk for stroke. Patients will be enrolled in up to 3 cohorts of approximately 16 patients each. After a Screening Period of up to 4 weeks, patients in will be randomized in a 3:1 ratio (MAA868:placebo) to receive 3 monthly subcutaneous (s.c.) injections and followed for pharmacokinetics, pharmacodynamic efficacy as well as safety events over the 90-day Treatment Period. Patients will then be followed up to Day 170 during the Washout/Follow-up period.

Number of patients:

Approximately 48 patients will be randomized into the study.

Diagnosis and main criteria for inclusion and exclusion:

Inclusion Criteria

- Male and female patients ≥ 18 and < 85 years old
- Current AF or atrial flutter on 12 lead electrocardiography at Screening
  or
  a history of paroxysmal AF (PAF) or atrial flutter as documented by prior telemetry, 12 lead electrocardiography or ambulatory (e.g. Holter or patch) monitor which is not due to a reversible condition (e.g. alcohol binge drinking)
- A CHA2DS2-VASc risk score of 0-1 for men and 1-2 for women and in whom, in the investigator's judgment, the use of an anticoagulant for stroke prevention is not indicated
- Body weight between 50 and 130 kg, inclusive

Exclusion criteria

- History of stroke, transient ischemic attack or systemic embolism
- History of major bleeding during treatment with an anticoagulant or antiplatelet therapy. (Patients who have had major bleeding on anticoagulants or antiplatelet therapy more than a year ago can be enrolled only if the bleeding was due to a reversible cause, e.g. gastro-duodenal ulcer, that was successfully treated)
- History of traumatic or non-traumatic intracranial, intraspinal or intraocular bleeding.
- Known bleeding diathesis or any known active bleeding at screening or baseline
- Family history of bleeding disorder
- Known active GI lesions predisposing to bleeding events
- Myocardial infarction, unstable angina pectoris or coronary artery bypass graft (CABG) surgery within 12 months prior to the screening period
- Clinically significant moderate or greater mitral stenosis severity (valve area <1.5 cm^2)
- Prosthetic heart valve
- Uncontrolled hypertension defined as SBP/DBP ≥ 160/100 mmHg at the screening visit
- NYHA class III-IV heart failure
- Currently being treated with anticoagulant therapy or have been on anticoagulants in the previous 12 months. Potential patients who have been on anticoagulation more than 12 months ago requires discussion with the sponsor before enrolling.
- Currently being treated with antiplatelet therapy such as a P2Y12 inhibitor or aspirin. Low dose aspirin (≤ 100 mg/d) is allowed
- Severe renal impairment as defined as an estimated glomerular filtration rate ≤45 mL/min/1.73m^2 by the MDRD equation at the screening visit
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception

Test products, dose, and mode of administration:
MAA868 with a dose of 120 mg or 180 mg or placebo s.c. monthly

Reference therapy, dose, dose form, and mode of administration:
Matching placebo to MAA868 s.c. monthly

Duration of patient participation in study:
Planned Screening duration: Up to 4 weeks
Planned treatment duration: Day 0-91: 91 days
Planned follow-up duration: Day 91 to Day 170: 79 days

Study populations:
Approximately 48 male and female patients age ≥ 18 to < 85 with AF or flutter, as defined above, will be randomized into the study.

Evaluation: Efficacy
- Free FXI concentrations at Days 31, 61 and 91

Evaluation: Safety
- Confirmed major bleeding events, clinically relevant non-major (CRNM) bleeding events and total bleeding events
- Adverse and serious adverse events
- Occurrence of major cardiovascular, cerebrovascular, systemic arterial, and
- Physical examinations
- Monitoring of laboratory parameters in blood
- ECGs
- Hypersensitivity reactions
- Injection site reactions

Evaluation: Other assessments
- Factor XI coagulation activity
- Activated partial thromboplastin time
- Pharmacokinetics
- Development of anti-drug antibodies
- Venous thromboembolic events

Statistical methods:
The patients will be enrolled into cohorts of approximately 16 patients with each cohort evaluating a different dose level of MAA868. Within each cohort, patients will be randomized 3:1 to active drug or placebo.
The primary analysis variable is whether a subject will achieve pre-defined degrees of FXI inhibition at trough (Day 91). The dose regimens and targeted FXI inhibition achievement are as follows:
Low-dose cohort (MAA868 120 mg monthly or placebo): Targeted to achieve ≥ 50% FXI inhibition in 90% of subjects at trough (Day 91).
High dose cohort (MAA868 180 mg monthly or placebo): Targeted to achieve ≥ 90% FXI inhibition in 90% of subjects at trough (Day 91).
The "on treatment" trough FXI levels will be used for the primary analysis, where "on treatment" FXI level is defined as a value which is collected within 30 (±5) days after the last administration of MAA868. The response rate per treatment group will be calculated by number of subjects who achieve targeted FXI inhibition rate divided by the total number of subjects in the treatment group. The estimate of the responder rate (%) at Day 91 will be presented for each dose regimens of MAA868 together with 2-sided 90% confidence intervals.
The secondary efficacy analysis is to evaluate the proportion of subjects achieving FXI inhibition ≥ 50%, ≥80%, and ≥90% at trough after the first and second dose (Day 31 and Day 61) at multiple dose levels of MAA868. The analyses described for the primary endpoint will be repeated for the secondary efficacy variables.
Safety data including adverse events (AEs), bleeding events, ECG, vital signs, thromboembolic events and laboratory results will be reported by count and incidence rate.

1. INTRODUCTION

1.1. Background

AF is the most common cardiac arrhythmia, accounting for approximately one third of hospitalizations for cardiac dysrhythmias. Currently, it is estimated to affect more than 6 million patients in Europe and approximately 2.3 million in the United States, and this number continues to grow rapidly because of the increasing proportion of the aging population with associated co-morbidities. As such, the prevalence of AF is expected to increase 2- to 3-fold over the following 3 decades in western populations (Kannel and Benjamin 2008).

AF is associated with a 4- to 5-fold increase in embolic stroke. The risk for stroke associated with AF increases steeply with age to 23.5% for patients aged 80 to 89 years (Kannel and Benjamin 2008). Most patients with AF require life-long anticoagulation therapy to prevent cardioembolic stroke and systemic embolism. It is estimated that 85 to 90% of AF patients will require anticoagulation therapy (Camm et al 2012).

Vitamin K antagonists (VKA), such as warfarin, are effective in reducing stroke and systemic thromboembolism; a highly significant relative risk reduction in stroke incidence by 67% was observed in a meta-analysis combining six studies (Hart et al 1999). All-cause mortality was reduced (26%) significantly by VKA vs. control (Hart et al 1999). In recent years, direct oral anticoagulant (DOACs) medications have been approved and introduced to clinical practice. These drugs are at least as effective as warfarin in preventing stroke or systemic embolism and may be superior to warfarin in the risk of hemorrhagic stroke and intracranial hemorrhage (Connolly et al 2009, Granger et al 2011, Patel et al 2011). The incidence of major bleeding events with DOACs was similar or slightly lower than the incidence observed with well-conducted warfarin therapy. Nonetheless, the overall bleeding risk continues to be high with the use of DOACs. For instance, the annual incidence of major and clinically relevant non-major (CRNM) bleeding was 14.9% and the annual incidence of major bleeding events was 3.6% in patients treated with rivaroxaban in the ROCKET AF study (Patel et al 2011). It is notable that the occurrence of major bleeding was strongly associated with mortality. In the same study, the rate of all-cause mortality over the 2-month period following a major bleeding event was 20.4% in the rivaroxaban group and 26.1% in the warfarin group (Piccini et al 2014). Thus, there is a high unmet medical need for an anticoagulant therapy that can effectively reduce the risk of AF-related thromboembolic complications such as stroke but with a lower risk of bleeding than currently employed anticoagulants.

FXI is an emerging target for potentially safer and more effective anticoagulant medications. FXI holds important roles in both the intrinsic and extrinsic coagulation pathways and in bridging the initiation and amplification phases of plasmatic hemostasis (Gailani and Renné 2007). Both Factor XII and thrombin can activate FXI, resulting in a sustained thrombin generation and fibrinolysis inhibition. FXI plays a minor role in normal hemostasis in a high tissue factor environment “after vessel injury” whereas it appears to play a key role in thrombosis. Severe FXI deficiency is associated with a lower incidence of ischemic stroke and venous thromboembolic events (Salomon et al 2008, Salomon et al 2011, Preis et al 2017). Nevertheless, bleeding manifestations in subjects with severe FXI deficiency are infrequent and usually mild. Bleeding events that occur are typically injury-related and preferentially affect tissues known to have increased fibrinolytic

activity such as the oral and nasal mucosa, and urinary tract (Bolton-Maggs 2000). Bleeding in vital organs is extremely rare or non-existent.

MAA868

MAA868 is a human antibody that binds to the catalytic domain of FXI. MAA868 binds to both the zymogen (FXI) and activated factor XI (FXIa) with high potency. MAA868 dose-dependently prolonged activated partial thromboplastin time (aPTT) in in-vitro and in-vivo studies. After a single subcutaneous (s.c.) administration of MAA868 at a 3 mg/kg dose, sustained anticoagulant activity lasting for more than one month was observed in cynomolgus monkeys. Moreover, MAA868 prevented experimental carotid artery thrombosis induced by FeCl3 and resulted in a prolongation in aPTT in FXI-/- mice reconstituted with human FXI. No significant toxicity findings were observed in single dose and in the 13-week Good Laboratory Practice (GLP)-compliant toxicity study conducted in cynomolgus monkeys. The highest s.c. dose administered in the 13-week study was defined as no observed adverse effect level NOAEL (100 mg/kg/week s.c.).

MAA868 was evaluated in a first-in-human (FIH) study (CMAA868X2101) to characterize its safety/tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) in healthy subjects following single s.c. administration. In total, 6 cohorts with 10 subjects each (8 MAA868: 2 Placebo) were enrolled. The doses of MAA868 administered in Cohorts 1 to 5 ranged from 5 mg to 240 mg. In a sixth cohort, 240 mg of MAA868 was administered to subjects with body mass index (BMI $\geq$ 35 kg/m2).

In the FIH study, MAA868 appeared to be safe and well tolerated, and the incidence of AEs were comparable across dose groups and placebo. No bleeding events, hypersensitivity reactions or injection site reactions were reported. Exposure increased with increasing dose of s.c. MAA868; the median maximum observed concentration (C_{max}) occurred on Day 7 to 21 and the mean terminal elimination half-life ranged from 20 to 28 days. A dose and time-dependent prolongation of aPTT occurred with MAA868 after single s.c. administration; the 150 mg dose resulted in a mean aPTT prolongation $\geq$ 2-fold at Day 29. Doses greater than 150 mg extended the duration of aPTT prolongation but did not produce a greater prolongation of aPTT. Robust and sustained reductions of free FXI $\geq$ 90% were observed with 150 mg MAA868 at Day 29 and up to Day 43 with 240 mg. A high BMI was associated with a lower MAA868 exposure and slightly shorter duration of aPTT prolongation. Robust reductions in free FXI and in FXI coagulation activity and relevant aPTT prolongation are predicted to occur within 12 to 24 hours after MAA868 s.c. administration with relevant clinical doses.

MAA868 was also studied in healthy Japanese subjects in a single ascending dose, randomized, subject- and investigator-blinded, placebo-controlled, non-confirmatory study to assess safety, tolerability, PK and PD. Three cohorts (MAA868 dose levels: 15, 50 and 150 mg) were enrolled in this study and received a single s.c. dose of MAA868 or matching placebo (8 subjects received MAA868 and 2 subjects received placebo in each cohort). Assessments and assessment schedules were generally similar to the FIH study. No SAE or study discontinuation due to AEs were reported in this study. All AEs were mild in intensity and the distribution of AEs was well balanced between the MAA868 dose groups and placebo. No bleeding event, hypersensitivity or injection site reactions were reported in the study. PK analysis suggested that there was no indication of an impact of the Japanese ethnicity on exposure or PD parameters of MAA868 in healthy subjects.

Taken together, the results from both completed studies of MAA868 suggest that the administration of MAA868 is safe and well-tolerated. Subcutaneous administration of MAA868 leads to robust and sustained effects on aPTT, free FXI, and FXI coagulation activity (FXI:C) up to/through Day 29 with the 150 mg dose and Day 43 with the 240 mg dose in subjects with normal body weight or class 1 obesity (BMI <35 kg/m2). In subjects with class 2 or 3 obesity (BMI ≥35 kg/m2), exposures of MAA868 may be lower and the duration of aPTT prolongation is shorter.

1.2. Study Rationale

This study is a multicenter, randomized, subject and Investigator-blinded, placebo-controlled, parallel-group, multiple ascending dose-ranging study to evaluate the safety, tolerability, PK, and PD effects of MAA868 in patients with AF or flutter at low risk of thromboembolic stroke or peripheral embolism. The trial will evaluate the effects of up to three different doses of MAA868 on FXI inhibition, indices of coagulation, and thrombogenesis biomarkers compared to placebo. The incidence of injection site reactions, bleeding events, immunogenicity, and systemic arterial and venous thromboembolic events will also be assessed. Results from this study will assist with dose-selection of MAA868 for a phase 3 trial in patients with AF.

1.3. Benefit-risk Assessment

AF is associated with a 4- to 5-fold increase in embolic stroke. MAA868, a fully human monoclonal antibody targeting Factor XI, is being considered for development as a novel anticoagulant for patients with AF or flutter. FXI is an emerging target as a novel anticoagulant. Several lines of evidence suggest that FXI inhibition has the potential to prevent thrombosis with minimal risk of bleeding. For example, individuals with an inherited deficiency of FXI have been reported to have a lower risk of VTE even though their bleeding phenotype is variable and often quite mild. Further support of the safety of inhibiting FXI comes from clinical studies using an investigational FXI antisense oligonucleotide (FXI-ASO) where administration of FXI-ASOs in healthy subjects and in patients undergoing total knee arthroplasty was demonstrated to be safe and well-tolerated (Buller et al 2015).

Results from the first-in-human (FIH) study of MAA868 (CMAA868X2101) demonstrated that a single s.c. administration of MAA868 at increasing doses up to 240 mg in healthy subjects were safe and well-tolerated. These doses of MAA868 resulted in a robust and sustained FXI inhibition and prolongation of aPTT. The safety and pharmacodynamic efficacy of MAA868 was further supported by preliminary data from the study CMAA868A1101, which showed a good safety profile of MAA868 in Japanese heathy male subjects.

This study is designed to evaluate the efficacy and safety of achieving different levels of FXI inhibition with different dose levels of s.c. MAA868 in patients with AF or flutter. This study will recruit patients with AF or flutter who are judged by their physician to be at low risk for stroke based on clinical guidelines. In each case, patients will ***only*** be enrolled if their physician has determined that the patient does not merit anticoagulation based on the guidelines and the physician's assessment of the benefit-risk profile for that patient. The guidelines state that the benefits of anticoagulation in AF patients at low risk of embolic stroke are uncertain given the concomitant risks of bleeding with anticoagulant therapy. Accordingly, the guidelines recommend individualized shared physician-patient decision-making with regards to the decision to initiate anticoagulant therapy in this population (January et al 2019). Patients with PAF will be enrolled who have a CHA2DS2-VASc risk score of 0-1 for men or 1-2 for women, in whom the guidelines

are equivocal regarding the recommendation to initiate anticoagulation and advise an individualized assessment of the benefit-risk of anticoagulation (January et al 2019).

Overall, the nonclinical and clinical data to date support the investigation of MAA868 in the prevention of thromboembolic diseases in patients with AF. The risk-benefit relationship appears to be acceptable.

2. OBJECTIVES AND ENDPOINTS

2.1. Primary objective and endpoint

Objective	Endpoint
• To evaluate the proportion of patients that achieve ≥50%, ≥80%, or ≥90% FXI inhibition at trough after the third dose (Day 91) at different dose levels of MAA868	• Occurrence of achieving ≥50%, ≥80%, or ≥90% inhibition of FXI (<50%, <20%, or <10% free FXI) at trough on Day 91 at different dose levels of MAA868

2.2. Secondary objectives and endpoints

Objective	Endpoint
• To evaluate the proportion of patients achieving FXI inhibition ≥50%, ≥80%, and ≥90% at trough after the first and second dose (Day 31 and Day 61) at different dose levels of MAA868	• Occurrence of achieving ≥50%, ≥ 80%, and ≥90% inhibition of FXI (<50%, <20%, or <10% free FXI) at trough on Day 31 and Day 61 at different dose levels of MAA868
• To evaluate the safety and tolerability following multiple s.c. administration of MAA868 compared to placebo in patients with AF	• All safety endpoints [i.e., physical exam, vital signs, electrocardiogram (ECG), safety laboratories, hypersensitivity reactions, injection site reactions, and adverse events (AEs), including serious AEs (SAEs)] during the Treatment Period and through EoS
• To evaluate the incidence of major bleeding events, clinically relevant non-major (CRNM) bleeding events and total bleeding with MAA868 relative to placebo during the treatment period	• Occurrence of confirmed major bleeding events, CRNM bleeding events and total bleeding events during the treatment period
• To evaluate the immunogenicity of MAA868 compared to placebo.	• Screening and confirmation for anti-drug (MAA868) antibodies (ADA)

2.3. Exploratory objectives and endpoint

Objective	Endpoint
• To evaluate the effect of MAA868 compared to placebo on the incidence of major cardiovascular, cerebrovascular, and venous thromboembolic events (as defined to the right)	• Occurrence of major cardiovascular, cerebrovascular, systemic arterial, and venous thromboembolic events (VTEs)

• To evaluate the change from baseline in D-dimer and other thrombogenesis markers with MAA868 relative to placebo during the treatment period	• Concentrations of D-dimer and other exploratory thrombogenesis markers during the treatment period

3. INVESTIGATION PLAN

3.1. Overall Study Design and Plan Description

This is a phase 2a, randomized, subject- and investigator-blinded, placebo-controlled, multiple ascending dose-ranging study to assess the PK/PD, safety, tolerability, and immunogenicity of MAA868 in patients with AF or flutter.

Patients will be enrolled in at least 2 and up to 3 cohorts of approximately 16 patients each for a total of up to 48 subjects (Figure 1A). Patients in cohort 1 will be randomized 3:1 to receive a 120 mg dose of MAA868 or placebo, respectively on Day 1 with two subsequent monthly injections. After approximately 10 of the patients in cohort 1 have received their second dose of study drug and have been followed for at least an additional 14 days, a safety review of emerging safety and PK data from cohort 1 will take place. Cohort 2 will be initiated after it is confirmed by the Sponsor's Medical Monitor and the Covance Lead Project Physician that the cohort 1 dose was safe and tolerated and all cohort 1 patients have been randomized. Likewise, after 10 of the patients in cohort 2 have received their second dose and have been followed for at least an additional 14 days, interim safety, tolerability, and other analyses will be evaluated by the Sponsor. Based on emerging data, the Sponsor may elect to:

- Enroll cohort 3 to evaluate a higher, lower, or a previously studied dose of MAA868
- Terminate the study

The study is comprised of 3 periods:

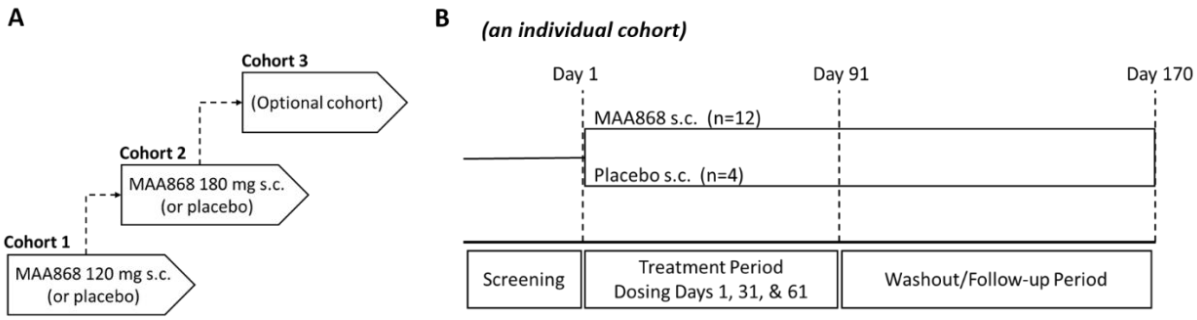
(1) Screening period of up to 4 weeks

(2) Treatment period with MAA868 administered s.c. monthly (or matching placebo) (randomized 3:1) for 90 days

(3) Follow-up period up to end of study (Day 170).

Following the screening period of up to 4 weeks, all patients that meet the study eligibility criteria (Section 4.1 and Section 4.2) will have baseline efficacy and safety assessments performed on Day 1 and then randomized to active or placebo (Figure 1B).

Figure 1: Overall study design



The first dose of study drug will be administered at the study center on Day 1. The second and third doses of study drug will also be administered at the study center to patients on the Day 31 visit and Day 61 visit, respectively.

During the treatment period, patients will return to the study center on Day 11, Day 31, Day 41, Day 61, Day 71, and Day 91 for safety assessments such as vital signs, AE assessments, laboratory tests, PK, PD, thrombogenesis biomarkers, and other study assessments according to the assessment schedule shown in Table 9.

During the follow-up period, patients will continue to be followed for PK, PD, thrombogenesis, and other study assessments. Patients will return to the study center on Day 101, Day 121 and Day 170 (end of study; EoS) for the evaluations described in the assessment schedule (Table 9).

3.2. Discussion of Study Design, Including the Choice of Control Groups

Rationale for route of administration and treatment duration. The s.c. route of administration was chosen because it is the route of administration anticipated for subsequent studies in patients with AF. In the FIH study of MAA868, the half-life of MAA868 ranged from 20-28 days following s.c. administration. Furthermore, a sustained PD effect of >2-fold mean activated partial thromboplastin time [aPTT] prolongation was observed for ~30 days and returned to the baseline level by ~60 days post-dose after a single 150 mg s.c. dose administration in study X2101. These data support monthly administration of MAA868. Furthermore, assessment of the exposure-response relationship of MAA868 in healthy subjects demonstrated a nearly flat exposure-response for relevant PD parameters (aPTT, FXI coagulation activity and free FXI) at concentrations above 4 µg/mL which is consistent with the Day 29 total MAA868 concentrations achieved with the 150 mg single dose administration in healthy subjects (CMAA868X2101).

Given the half-life of MAA868 and the observed time to return to baseline aPTT levels, a prolonged washout/follow-up period of approximately 110 days from the last dose of MAA868 should be a sufficient monitoring period for patients.

3.3. Selection of Doses in the Study

In the FIH study, single s.c. doses of MAA868 up to 240 mg was safe and well-tolerated. Up to the 150 mg dose, MAA868 produced robust and sustained dose-dependent inhibition of FXI and relevant prolongation of aPTT for approximately 4 weeks. MAA868 doses greater than 150 mg s.c. produced a sustained ~2-fold prolongation of aPTT for greater than 4 weeks.

The precise level of FXI inhibition to achieve a clinically meaningful anticoagulant effect remains unknown. The primary efficacy endpoint of this study will be the number of patients who achieve ≥ 50%, ≥ 80%, or ≥ 90% FXI inhibition [<50%, <20%, or 10% free FXI] at trough on Day 91 following s.c. administration of MAA868. Based on preliminary PK/PD modeling, the doses selected for cohorts 1 and 2 are projected to target the following levels of FXI inhibition:

- Cohort 1 (120 mg dose group). Targeted to achieve ≥ 50% FXI inhibition in 90% of subjects at trough (Day 91).
- Cohort 2 (180 mg dose group). Targeted to achieve ≥ 90% FXI inhibition in 90% of subjects at trough (Day 91).

Based on interim data, an optional cohort 3 may be dosed to add further data to the PK/PD model which will inform dose selection of MAA868 for subsequent studies.

The dosing regimens selected for evaluation in this study are projected to result in exposure (C_{max}) below the C_{max} achieved with a single dose of 240 mg s.c. in healthy subjects in the FIH study.

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

1. Written informed consent must be obtained before any assessment is performed
2. Male and female patients ≥ 18 and < 85 years old with paroxysmal atrial fibrillation (PAF) or atrial flutter on 12 lead electrocardiography at Screening Or
3. Patients with a history of PAF or atrial flutter, as documented by (telemetry, 12 lead electrocardiography or ambulatory [e.g. Holter] monitor) and not due to a reversible condition (e.g. alcohol binge drinking) can be entered even if they do not have PAF at Screening. There is not time-limit for this.
4. Patients with a CHA2DS2-VASc risk score (tool as a predictor for estimating the risk of stroke in patients with AF; Lip et al 2010) of 0-1 for men and 1-2 for women and in whom, in the investigator's judgment, the use of an anticoagulant for stroke prevention is not indicated
5. Body weight between 50 and 130 kg inclusive

4.2. Exclusion Criteria

1. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or until the expected PD effect has returned to baseline, whichever is longer; or longer if required by local regulations.
2. History of stroke, transient ischemic attack or systemic embolism
3. History of major bleeding during treatment with an anticoagulant or antiplatelet therapy. (Patients who have had major bleeding on anticoagulants or antiplatelet therapy more than a year ago can be enrolled only if the bleeding was due to a reversible cause, e.g. gastro-duodenal ulcer that was successfully treated.)
4. History of traumatic or non-traumatic intracranial, intraspinal or intraocular bleeding
5. Known bleeding diathesis or any known active bleeding site at screening or baseline
6. Family history of bleeding disorder
7. Known active GI lesions predisposing to bleeding events
8. Myocardial infarction, unstable angina pectoris or coronary artery bypass graft (CABG) surgery within 12 months prior to the Screening period
9. Known clinically significant valvular heart disease including moderate or severe mitral stenosis (valve area <1.5 cm^2).
10. Patients with a prosthetic heart valve
11. Uncontrolled hypertension defined as SBP/DBP ≥ 160/100 mmHg at the Screening visit
12. Patients with NYHA Class III- IV heart failure
13. Currently being treated with anticoagulant therapy or have been on anticoagulants in the previous 12 months. Potential patients who have been on anticoagulation more than 12 months ago requires discussion with the sponsor before enrolling.
14. Treatment with antiplatelet therapy such as either a P2Y12 inhibitor or aspirin. (Low dose aspirin ≤ 100 mg/d) is allowed.)
15. Severe renal impairment as defined as an estimated glomerular filtration rate ≤45 mL/min/1.73m^2 by the MDRD equation at the Screening Visit

16. Positive test for human immunodeficiency virus (HIV), positive hepatitis B (hepatitis B surface antigen [HBsAg]) or hepatitis C (anti-hepatitis C antibody [Anti-HCV]) at Screening
17. Significant illness, per Investigator judgement, which has not resolved within four (4) weeks prior to dosing
18. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during their time in the study. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment
    - Male sterilization of sexual partner (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
    - Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception

    In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.
    Women are considered post-menopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment with FSH is she considered not of child-bearing potential. Male subjects must also agree to use highly effective methods of contraception during their time in the study and should not father a child or donate sperm in this period.
19. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
20. Patients with either a psychiatric disease or substance abuse history, which in the opinion of the Investigator could interfere with protocol compliance.
21. Any surgical or medical condition, which in the opinion of the Investigator, may place the patient at higher risk from his/her participation in the study, or is likely to prevent the patient from complying with the requirements of the study or completing the study.

4.3. Discontinuation Criteria

4.3.1. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Patients who do not meet the criteria for participation in this study may be rescreened.

4.3.2. Withdrawal of informed consent

Subjects may voluntarily withdraw from the study for any reason at any time.

Withdrawal from the study can occur when a subject chooses to do one or more of the following:

- Does not want to participate in the study anymore
- Does not want any further visits or assessments
- Does not want any further study-related contacts
- Does not allow analysis of already obtained biologic material.

If a subject who has received one or more doses of the study drug determines that they no longer want to participate the Investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason(s) for the subject's decision to withdraw his/her consent, record this information and conduct any assessments and visits still allowed.

In the event the subject withdraws consent prior to beginning dosing, the study treatment will not be administered. The data that would have been collected at subsequent visits will be considered missing. Further attempts to contact the subject are allowed when safety findings require follow-up.

4.3.3. Lost to Follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the Investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject cannot be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

4.4. Stopping Rules

Overall study stopping rules:

Enrollment in the study will be placed on hold if the Sponsor considers that the number and/or severity of AEs, abnormal safety monitoring tests or abnormal laboratory findings justify putting the study on hold.

The study may resume following the safety review, if the Investigator and Sponsor's Medical Monitor agree it is safe to proceed.

5. STUDY TREATMENTS

5.1. Treatments Administered

MAA868 drug product is a sterile, preservative-free liquid in vial for subcutaneous (s.c.) or intravenous (i.v.) administration. Each drug product vial contains 150 mg of MAA868 active ingredient per 1 mL plus 20% (0.2 mL) overfill which allows for complete withdrawal of the labeled dose (150 mg). [redacted] The excipients utilized are standard pharmacopoeial excipients that are commonly used in parenteral products. MAA868 will be provided as a 150 mg/mL solution in 6 mL single-use vials (with 1.2 mL fill). The 180 mg dose will require 2 vials. 0.8 and 1.2 mL should be withdrawn into a syringe and administered subcutaneously for the 120 mg and 180 mg doses, respectively.

Table 1: Overview of Study Medication

Study Treatment Name:	MAA868	Placebo
Dosage Formulation:	Liquid (in vial)	Liquid (in vial)
Unit Dose Strength(s)/Dosage Level(s):	150 mg/mL	Placebo to MAA868
Route of Administration:	SC injection	SC injection
Packaging and Labeling:	Study Treatment will be provided in vials. Each vial will be labeled as required per country requirement.	Placebo will be provided in vials. Each vial will be labeled as required per country requirement.
Provided by:	Anthos	Anthos

5.2. Preparation, Storage, Handling, and Accountability

Details on the requirements for storage and management of study treatment, and instructions to be followed for subject numbering, prescribing/dispensing and administering study treatment are outlined in the Pharmacy Manual.

MAA868 drug product vials should be stored refrigerated at 2°- 8°C and protected from light. A disposable syringe will be used to administer the s.c. injection.

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment. Only patients enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study treatment are provided in the Pharmacy Manual.

5.3. Method of Treatment Assignment

Subjects in each cohort will be randomized to MAA868 or placebo in a ratio of 12: 4 as follows.

- Cohort 1 = 120 mg MAA868 monthly s.c. or placebo
- Cohort 2 = 180 mg MAA868 monthly s.c. or placebo
- Cohort 3 (if necessary) = TBD mg MAA868 monthly s.c. or placebo

Randomization numbers will be assigned in ascending, sequential order to eligible subjects. The Investigator will enter the randomization number on the CRF.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A randomization list will be produced by or under the responsibility of Covance Drug Supply Management using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio. The randomization scheme for subjects will be reviewed and approved by a member of the Covance IIS Randomization Group.

Patients will be replaced at the Sponsor's discretion. Replacement subjects will be assigned randomization numbers 6101-6316 If a subject requires a replacement, the replacement subject will be assigned a randomization number corresponding to the original subject (e.g., Subject 6103 would replace Subject 1103).

The table below provides the general details of the numbering of the subjects for randomization:

Table 2: Randomization Assignment Numbering

Cohort	Randomization numbers	Replacement randomization numbers
I	1101-1116	6101-6116
II	1201-1216	6201-6216
III	1301-1316	6301-6316

5.4. Blinding

This is a subject- and investigator-blinded study. Subjects will remain blinded to study treatment throughout the study, except where indicated below.

The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

Site staff

With the exception of any unblinded pharmacist or pharmacy designee, all site staff (including study investigator and study nurse(s)) will be blinded to study treatment during treatment allocation and subject dosing. Appropriate measures must be taken by any unblinded pharmacist or pharmacy designee to ensure that the treatment assignments are concealed from the rest of the site staff.

Unblinding a single subject at the site for safety reasons (necessary for subject management) will occur via an emergency system in place at the site (see Section 5.10).

Site staff may also be unblinded to the treatment assignment of one or more subjects (within a single cohort or across cohorts as necessary), or an entire cohort at the initial cohort safety

evaluation timepoint if deemed appropriate to aid decision-making. The decision to un-blind site staff will be determined by the clinical trial team based on need or review of the entire study group will be performed at a pre-selected time.

Sponsor staff

The following unblinded Sponsor roles (or designee) are required for this study:

- Field monitor(s) (evaluation of drug dispensing and reconciliation)
- Physician not directly involved in study conduct
- Sample analyst(s) (PK blood)
- Study statistician
- Programmers and other personnel involved in study data analysis

An unblinded Covance Physician not directly involved in study conduct may receive a copy of the randomization schedule (via request to the Randomization Office), to facilitate analysis of aPTT safety labs that would otherwise unblind study Investigators. The unblinded Medical Monitor will alert the Investigator and Sponsor of any safety concerns.

The sample analysts will receive a copy of the randomization schedule (via request to the Randomization Office), to facilitate analysis of the samples. The sample analysts will provide the sample data to the study team under blinded conditions unless otherwise allowed.

The study statistician will be able to access the full randomization list from the start of the study and is allowed to share unblinded information with the rest of the clinical trial team as appropriate for internal decision purposes. For example, unblinded summaries and unblinded individual data can be shared with the team whenever necessary.

Study programmers and other personnel involved in study data analysis (e.g. biomarker expert, pharmacometrician, modeler(s)) are allowed to access treatment assignment information from the start of the study for the purpose of data analysis.

The clinical trial team is allowed to share unblinded results with other Sponsor staff (e.g. decision boards) as required for internal decision making on the study or the project while the study is ongoing.

All unblinded personnel will otherwise keep randomization lists and data or information that could un-blind other study team members confidential and secure except as described above.

Following final database lock all roles may be considered unblinded.

5.5. Treating the subject

MAA868 will be administered to the subject by study staff via s.c. administration. See the Pharmacy Manual for further details.

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

5.6. Permitted dose adjustments and interruptions of study treatment

Study treatment dose adjustments are not permitted. Any study drug administration that occurs outside of study visit windows must be approved by the study medical monitor.

5.7. Study Completion and Post-study Treatment

Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them.

Study completion is defined as when the last subject completes their EoS visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

All subjects will be required to attend the EoS visit and have related assessments collected as per the Schedule of assessments (Table 9). All SAEs reported during this time period must be reported as described in Section 7.6.2 and the Safety Management Plan. Documentation of attempts to contact the subject should be recorded in the source documentation.

5.8. Discontinuation of Study Treatment

The Investigator may decide to suspend the s.c. administration of the study drug if symptoms or signs consistent with an injection site reaction or hypersensitivity reaction occur.

Subjects who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 4.3.2, Withdraw of Informed Consent). Where possible, they should return for the EoS assessments indicated in the assessment table. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in Section 4.3.3 (Lost to follow-up). This contact should preferably be done according to the study visit schedule.

5.9. Study Termination

The study can be terminated by Anthos at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. Should this be necessary, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject and followed until the aPTT has returned to baseline. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The Investigator will be responsible for informing the Institutional Review Board (IRB) of the early termination of the trial.

5.10. Emergency breaking of assigned treatment code

Emergency unblinding must only be undertaken when it is essential to treat the subject safely and efficaciously, such as in the event of clinically significant bleeding events. Most often, knowledge of the possible treatment assignments is sufficient to treat a study subject who presents with an emergency condition. A complete set of emergency code break cards will be provided to the Investigator site(s) and a complete set will be available at Anthos and Covance. All code break cards must be retained until the end of the study and retained by the site as a source document.

They must be stored in a secure place but be accessible to the Investigator 24 hours per day in case of emergency. The Investigator will receive a blinded code break card for each subject. In an emergency, the code break may be opened to determine the treatment. There is no known reversal agent for MAA868 (see Section 6.2).

The code break should not be opened for any reason other than an emergency. If the Investigator opened the code break, he/she must note the date, time, and reason for removing it and retain this information with the case report form documentation. The unblinded treatment code must not be recorded on the CRF. The Investigator must also immediately inform the study monitor that the code has been broken.

It is the Investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the code break cards at any time in case of emergency. The Investigator will need to provide:

- Protocol number
- Study drug name (if available)
- Subject number.

In addition, the Investigator must provide oral and written information to inform the subject how to contact his/her backup in cases of emergency when he/she is unavailable to ensure that un blinding can be performed at any time.

6. CONCOMITANT THERAPIES

6.1. Concomitant therapy

The Investigator must instruct the subject to notify the study staff of any new medications (including nutritional supplements and herbal medications) that he/she takes after being enrolled into the study.

All prescription medications, OTC drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the Investigator should contact Covance before randomizing a subject or, if the subject is already enrolled, to determine if the subject should continue participation in the study.

During the study, in the event the Investigator elects to start the patient on chronic antithrombotic therapy, anticoagulation or antiplatelet therapy should not be started until the patient's aPTT has returned to baseline.

Reporting medication errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient/subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

All study treatment errors and uses outside of what is foreseen in the protocol will be collected in the Dose Administration Record CRF. Study treatment errors are only to be reported to Covance DSS department if the treatment error is associated with an SAE.

All instances of misuse or abuse must be documented in the AE CRF irrespective of the misuse/abuse being associated with an AE/SAE. In addition, all instances of misuse or abuse must be reported to the Covance DSS department. As such, instances of misuse or abuse are also to be reported using the SAE form/CRF. Table 3 summarizes the reporting requirements.

Table 3: Summary of reporting requirements for medication errors

Treatment error type	Document in Dose Administration CRF	Document in AE CRF	Complete SAE form/CRF
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see Section 7.6.1 and Section 7.6.2, respectively.

6.2. Study restrictions

Pregnancy and contraception

Women of child-bearing potential are not permitted to participate in this study, unless they agree to use highly effective methods of contraception during their time in the study.

During their time in the study, sexually active male subjects must agree to use highly effective methods of contraception and should not father a child or donate sperm in this period. **Prohibited treatment**

Use of the following medications is not allowed during the course of the study from screening (Visit 1) through the EoS. Patients who are receiving such medication(s) will be excluded, or if ethically and clinically justified, the medication(s) should be gradually withdrawn at least seven days before the baseline visit:

- Use of chronic antiplatelet agents such as clopidogrel or ticagrelor is prohibited; however, use of low-dose aspirin (≤100 mg per day) is permitted.
- Use of chronic systemic anticoagulants such as warfarin, low molecular weight heparin or heparinoids, or direct oral anticoagulants such as apixaban or dabigatran. Patients may be started on chronic anticoagulation during the Washout/Follow-up period once their aPTT has returned to baseline, at the Investigator's discretion.
- Use of any therapeutic monoclonal antibody regardless of the indication during the study.

Dietary restrictions

- No alcohol for 48 hours before each clinic visit (from Screening through the EoS visit). During the study, alcohol consumption will be restricted to no more than 2 drinks/day for males and 1 drink/day for females.
- Patients should not make significant alterations in their diet (e.g., going on weight loss diet) while in the study.
- During the study, caffeinated beverages will be restricted to no more than 3 cups/day.

Other restrictions

No strenuous physical exercise or activities which have an increased risk of injury or falling should be undertaken until after the EoS visit.

6.3. Reversal medication

There is currently no specific antidote for MAA868. FXI concentrates (not marketed in the US) are unlikely to be effective as the excess in free MAA868 concentrations in the circulation is expected to quickly neutralize the exogenous FXI.

Recombinant FVIIa can bypass the hypocoagulopathy and restore hemostasis in patients with severe FXI deficiency. Administration of intermediate to high doses of rFVIIa (40 to 90 µg/kg) resulted in supra-physiological levels of FVII and thromboembolic complications in patients with severe FXI deficiency (Riddell et al 2011). Low doses of rFVIIa are associated with lower prothrombotic risk. Riddell et al reported their experience in 4 patients with severe FXI deficiency undergoing surgery (Riddell et al 2011); patients were administered rFVIIa 30 µg/kg and tranexamic acid 1 g i.v. at induction of anesthesia. Subsequent bolus doses of rFVIIa 15–30 µg/kg were administered at 2 to 4 hourly intervals as guided by rotational thromboelastometry for 24 48 hours and tranexamic acid 1 g every 6 hourly for 5 days. Low doses of rFVIIa and tranexamic acid were safe and effective in restoring hemostasis in severe FXI deficiency in this study. In another study comprising 4 patients with severe FXI deficiency with inhibitor who experienced 5 surgeries (Livnat et al 2009), 1 g of tranexamic acid was given 2 hours before surgery, immediately prior to the interventions then every 6 hour for at least 7 days; moreover, rFVIIa was administered at doses ranging from 15 to 30 µg/kg at the completion of surgery. This protocol secured normal hemostasis in patients with severe FXI deficiency with inhibitor.

Based on the above, rFVIIa can be recommended as a preferred therapeutic option to restore hemostasis in subjects with active, non-accessible bleeding site and in subjects requiring immediate reversal of the MAA868 PD effects prior to an urgent surgery. Please see the Investigator's Brochure - Summary of the data and guidance for the investigator for a more complete discussion.

7. STUDY ASSESSMENTS AND PROCEDURES

7.1. Assessment schedule

Subjects should be seen for all visits/assessments as outlined in the assessment schedule (Table 9).

Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the study treatment discontinuation (TD) visit will be performed. At the TD visit, all dispensed investigational product should be reconciled, and the AE and concomitant medications recorded on the CRF.

7.2. Informed consent procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB-approved informed consent.

The Sponsor, or Sponsor designee, will provide to investigators a proposed informed consent form that complies with the ICHE6 Good Clinical Practice (GCP) guideline and regulatory requirements and is considered appropriate for this study. The informed consent form will also include a section related to optional future research which will require a separate signature if the subject agrees to future research. Any changes to the proposed consent form suggested by the Investigator must be agreed to by the Sponsor before submission to the IRB.

Information about common side effects already known about the investigational drug can be found in the IB. This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and then must be discussed with the subject.

Ensure subjects are informed of the contraception requirements outlined in the Section 4.2 (Exclusion criteria).

A copy of the approved version of all consent forms must be provided to the Covance monitor after IRB approval.

7.3. Subject screening

In general, it is permissible to re-screen a subject if s/he fails the initial Screening or falls out of the screening window timelines; however, each case must be discussed and agreed with the Sponsor Medical Monitor on a case-by-case basis. A new screening number will be assigned to a subject who is re screened, thus no screening number will be used twice.

Reasons for screen failure will be documented in the site log.

7.4. Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data will be collected on all subjects. Relevant medical history/current medical conditions data will also be collected until signature of informed consent.

Investigators have the discretion to record abnormal test findings on the medical history CRF, if in their judgment, the test abnormality occurred prior to the informed consent signature.

Hepatitis screen, HIV screen

All subjects will be screened for HIV, Hepatitis B and C.

Alcohol test and drug screening

All subjects will be screened for alcohol and substances of abuse.

7.5. Efficacy Assessments

The PD samples will be collected at the timepoints defined in the Assessment schedule (Table 9). Follow instructions outlined in the Central Laboratory Manual regarding sample collection, numbering, processing and shipment.

In order to better define the PD profile, the timing of the sample collection may be altered based on emergent data. The number of samples/blood draws and total blood volume collected will not exceed those stated in the Laboratory Manual.

PD samples will be obtained and evaluated in all subjects at all dose levels.

7.5.1. Free FXI

Free FXI concentrations (FXI that is not bound to MAA868) will be measured in plasma. A detailed description of the assay methods will be included in the Bioanalytical Data Report.

7.5.2. aPTT

aPTT, calibrated for FXI deficiency, and aPTT using a standard laboratory protocol will be measured at all timepoints indicated in the Assessment schedule (Table 9).

aPTT will be determined in plasma. The detailed method descriptions of the assay will be included in the Bioanalytical Data Report.

7.5.3. Total FXI

Total FXI concentrations (FXI that is either bound to MAA868 or free) will be measured in plasma. A detailed description of the assay methods will be included in the Bioanalytical Data Report.

7.5.4. FXI coagulation activity (FXI:C)

FXI:C will be measured in plasma. A detailed description of the assay methods will be included in the Bioanalytical Data Report.

7.6. Safety Assessments

Safety assessments are specified below; assessments will be collected as specified in the Assessment Schedule (Table 9).

Bleeding

All suspected bleeding events will be documented by the Investigator in the appropriate CRF. All suspected bleeding events will be adjudicated by experienced medical personnel that is blinded to

treatment assignment. Adjudication of bleeding events will be performed in accordance with the International Society of Thrombosis and Haemostasis (ISTH) definition of a major bleeding in non-surgical patients (Schulman et al 2005) and criteria for clinically-relevant non-major bleeding (CRNM) events. The definitions of bleedings are as follows:

Major bleeding events include:

- Fatal bleeding, and/or
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or
- Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more or leading to transfusion of two or more units of whole blood or red cells.

CRNMs (clinically relevant non-major) bleeding events will be defined as clinically overt bleeding that did not satisfy the criteria for major bleeding and that led to:

- hospital admission, or
- physician-guided medical treatment, or
- surgical treatment or
- change in antithrombotic therapy

In addition to the ISTH definition of bleeding events other definitions such as TIMI, BARC,

GUSTO, etc. can be used as supportive for exploratory safety analyses.

The population is those who have received at least one dose of the study drug.

Major cardiovascular, cerebrovascular, and venous thromboembolic events

All suspected major cardiovascular, cerebrovascular, and VTE events will be documented by the Investigator in the appropriate CRF including any diagnostic imaging that was used to confirm the event. For instance, any suspected episodes of DVT (i.e., swelling, localized pain, redness, heat, localized warmth) must be documented by compression ultrasound (CUS) or venography.

Any suspected episodes of PE (i.e., shortness of breath, chest pain, coughing, tachycardia, hemoptysis, hemodynamic compromise, unexplained death) must be documented by ventilation/perfusion lung scintigraphy, spiral computed tomography (sCT), or pulmonary angiography.

All major cardiovascular, cerebrovascular, systemic arterial, and venous thromboembolic events (VTEs) including deaths for which a major cardiovascular, cerebrovascular, or VTE event could not be ruled out will be adjudicated by experienced medical personnel that is blinded to treatment assignment.

The adjudicated outcome will be the basis for any interim and final safety evaluations.

7.6.1. Adverse Events

An AE is any untoward medical occurrence [i.e., any unfavorable and unintended sign (including abnormal laboratory findings), symptom or disease] in a subject or clinical investigation subject after providing written informed consent for participation in the study until the EoS visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the study treatment are also considered an AE irrespective if a clinical event has occurred. See Section 7.6.2 for an overview of the reporting requirements.

The occurrence of AEs must be sought by non-directive questioning of the subject at each visit during the study. AEs also may be detected when they are volunteered by the subject during or between visits or through physical examination finding, laboratory test finding, or other assessments.

Abnormal laboratory values or test results constitute AEs only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in healthy subjects. Investigators have the responsibility for managing the safety of individual subject and identifying AEs. Alert ranges for liver and kidney related events are included in Appendix 1 and Appendix 2, respectively. Additional clinically notable laboratory values are included in Appendix 3.

AEs must be recorded on the AE CRF under the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

1. Severity grade

- mild: usually transient in nature and generally not interfering with normal activities
- moderate: sufficiently discomforting to interfere with normal activities
- severe: prevents normal activities

2. Relationship to the study treatment

- Related
- Possibly related
- Not related

3. Duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.

4. Whether it constitutes a SAE (see Section 7.6.2 for definition of SAE) and which seriousness criteria have been met

5. Action taken regarding investigational treatment.

All AEs must be treated appropriately. Treatment may include one or more of the following:

- no action taken (e.g. further observation only)
- concomitant medication or non-drug therapy given
- hospitalization/prolonged hospitalization (see Section 7.6.2 for definition of SAE)

6. Outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown).

Information about common side effects already known about the investigational drug can be found in the IB. Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the investigational drug, the interventions required to treat it, and the outcome.

The Investigator must also instruct each subject to report any new AE (beyond the protocol observation period) that the subject, or the subject's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the Investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Covance.

7.6.2. Reporting Serious Adverse Events

Definition of SAE

An SAE is defined as any AE [appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s)] which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - elective or pre-planned treatment for a pre-existing condition and has not worsened since the start of study drug
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - social reasons and respite care in the absence of any deterioration in the subject's general condition
    - is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (see Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (see Annex IV, ICH-E2D Guideline).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All AEs (serious and non-serious) are captured on the CRF; SAEs also require individual reporting to Covance Drug Safety & Epidemiology (DS&E).

SAE Reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last planned study assessment, must be reported to Covance within 24 hours of learning of its occurrence as described below. Any SAEs experienced after this period should only be reported to Covance if the Investigator suspects a causal relationship to study treatment.

Note: SAEs reported by subjects deemed to be screen failures must be reported to Covance as outlined here with appropriate information also captured in the CRFs.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the Investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Follow- up information provided must describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable) and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the IB (new occurrence) and is thought to be related to the study treatment a Covance DS&E associate may urgently require further information from the Investigator for Health Authority reporting. Covance may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Follow the detailed instructions outlined in the Safety Management Plan regarding the submission process for reporting SAEs to Covance. Note: SAEs must be reported to Covance within 24 hours of the Investigator learning of its occurrence/receiving follow-up information.

7.7. Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events must be followed.

Please refer to Appendix 1 for complete definitions of liver events.

Follow-up of liver events

Every liver event defined in Appendix 1 should be followed up by the Investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 4 of Appendix 1.

- Repeating liver chemistry tests (ALT, AST, total bilirubin (TBL), PT/INR, ALP and γGT) to confirm elevation within 48-72 hours.

  These liver chemistry repeats should always be performed using the central laboratory, with the results provided via the standard electronic transfer. If results will not be available from the central laboratory within 24 hours, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results reported on the unscheduled local laboratory CRF.

- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to Section 4.3 (Discontinuation of study treatment), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
    - Repeating liver chemistry tests two or three times weekly. Testing should include ALT, AST, ALP, PT/INR, and γGT. If total bilirubin is elevated > 2 x ULN, fractionation into direct and indirect bilirubin is required. To rule out muscular origin of transaminase elevations, CPK should be measured along with liver chemistry tests. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic. Retesting should be continued up to resolution.
    - Obtaining a more detailed history of symptoms and prior or concurrent diseases.
    - Obtaining a history of concomitant drug use (including non-prescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.

- Exclusion of underlying liver disease, as specified in Table 6.
- Imaging such as abdominal US, CT or MRI, as appropriate
- Obtaining a history of exposure to environmental chemical agents.
- Considering gastroenterology or hepatology consultations.

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF.

7.8. Renal safety monitoring

Every renal laboratory trigger or renal event must be followed up by the Investigator or designated personnel at the trial site. Recommended follow-up assessments are listed in Appendix 2.

7.9. Pregnancy

All female study participants, regardless of the requirement to be of non-child-bearing potential to be enrolled into this study, will have pregnancy testing. See the Assessment Schedule (Table 9), for timing of the protocol required pregnancy testing; additional pregnancy testing may be performed to meet local requirements*. Subjects will not receive study medication in case of a positive urine or serum pregnancy test.

*If additional pregnancy testing is needed per local requirements, those additional results will be kept as source documentation only.

Pregnancy reporting

Reproductive toxicity and teratogenicity data are not available for this antibody at this time, therefore no guidelines on therapeutic recommendations in case of pregnancy are available. This study enrolls women who are considered to be of non-child-bearing potential, thus pregnancy is not an expected outcome for any female study participant. However, in the case that a pregnancy in a female study participant should occur please follow the below reporting guidelines. The follow-up for this subject and for the fetus is at the discretion of the Investigator.

To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Covance within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the Investigator to the local Covance DSS department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

All assessments that are considered as a risk during pregnancy must not be performed. The subject may continue all other protocol assessments.

7.10. Clinical Laboratory Evaluations

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Covance personnel. The results should be evaluated for criteria defining an AE and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Covance personnel should be contacted.

Safety labs (hematology, clinical chemistry and urinalysis) do not need to be repeated at baseline if the Baseline visit is taking place within 48 hours of the screening labs being collected from an individual subject.

Subjects should be instructed to fast for at least 8 hours prior to scheduled safety lab collections.

Clinically notable laboratory findings are defined in Appendix 3.

Hematology

Hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differentials and platelet count will be measured.

Clinical chemistry

Sodium, potassium, creatinine, BUN/urea, uric acid, chloride, albumin, calcium, alkaline phosphatase, total bilirubin, bicarbonate/HCO_3, LDH, GGT, AST, ALT, CK, glucose, total cholesterol, triglycerides. If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

Urinalysis

Dipstick measurements for specific gravity, protein, glucose and blood will be performed. Microscopy, WBC, RBC and sediments will also be assessed in case of an abnormal dipstick test.

Special clinical laboratory evaluations

Stool samples will be collected to check for occult blood at screening and baseline. Screening fecal samples can be collected at any time during the Screening period, and baseline fecal samples must be collected within 72 hours of Day 1. If fecal screening samples are collected within 72 hours of Day 1, then they do not need to be repeated for the Baseline visit. In the event that a subject is unable to produce a stool sample for sampling, the site medical staff may elect to produce a sample via digital extraction from the rectum.

Details regarding collection methods and processing are outlined in the Central Laboratory Manual.

7.11. Vital Signs, Physical Examination, and Other Safety Evaluations

Vital signs will include the collection of oral body temperature (recorded in °C), blood pressure (BP)–sitting and standing –and pulse measurements. At Screening, for eligibility determination, three sets of systolic and diastolic BP and pulse rate measurements will be collected after the subject has been sitting for 3 minutes, with back supported and both feet placed on the floor and

the mean will be used to determine eligibility. A single set of BP and pulse rate measurements will then be collected after three minutes in the standing position.

A single set of sitting BP measurements will be collected at subsequent visits.

Physical exams will include assessment of general appearance, skin, lymph nodes, HEENT, neck, thorax/lungs, cardiovascular, abdomen, musculoskeletal, and neurological systems.

Height in centimeters (cm) and body weight [to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes] will be measured. Body mass index (BMI) will be calculated using the following formula:

BMI = Body weight (kg) / [Height (m)]$_2$. BMI results will be documented in the CRF to 2 decimal places.

7.12. Electrocardiogram (ECG)

The ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. PR interval, QRS duration, heart rate, RR interval, QT, QT corrected by the Fridericia correction formula (QTcF) will be collected. The QTcF should be used for clinical decision-making. ECGs must be collected, analyzed and appropriately signed and archived at the study site; the site will also store all ECG readings digitally (if possible). For any ECGs with subject safety concerns, duplicate ECGs must be performed to confirm the safety finding. Clinically significant ECG findings at baseline must be discussed with the Sponsor before administration of study treatment. Clinically significant abnormalities must be reported in the AE CRF.

7.13. Pharmacokinetic Analysis

The PK samples will be collected at the timepoints defined in the Assessment schedule (Table 9). Follow instructions outlined in the Central Laboratory Manual regarding sample collection, numbering, processing and shipment. See Section 7.15 regarding the potential use of residual samples.

In order to better define the PK profile, the timing of the PK sample collection may be altered based on emergent data. The number of samples/blood draws and total blood volume collected will not exceed those stated in the Laboratory Manual. Changes to the PK Assessment schedule, if any, will be communicated to the sites in the dose adjustment minutes.

The PK samples will be obtained and evaluated in all subjects at all dose levels. Untreated (placebo) samples will not be analyzed.

Concentrations of plasma total MAA868 (i.e. MAA868 that is bound to FXI or not bound to FXI) will be determined by a validated LC-MS/MS method. A detailed description of the method used to quantify the concentration of total MAA868 will be included in the bioanalytical raw data and in the Bioanalytical Data Report.

All concentrations below the LLOQ or missing data will be labeled as such in the concentration data listings.

For standard PK abbreviations and definitions see the list provided at the beginning of this protocol.

The following PK parameters will be determined, where data permit, using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.2 or higher): C_0 (the concentration at the end of infusion), AUC_{last}, AUC_{inf}, C0/D, and AUC/D, based on the plasma concentration data.

The linear trapezoidal rule will be used for AUC calculation. The terminal half-life of MAA868 ($T_{1/2}$), volume of distribution (V_{ss}) and clearance (C_L) will also be estimated, if feasible, based on the data.

7.14. Other assessments

7.14.1. Exploratory Biomarker assessments

Biomarkers including, but not limited to, D-Dimer and biomarkers of thrombogenesis and coagulation may also be studied.

The list may be changed or expanded further, as it is recognized that more relevant or novel biomarkers may be discovered during the conduct of the study.

Sample(s) will be collected at the timepoint(s) defined in the Assessment schedule (Table 9).

Follow instructions for sample collection, numbering, processing and shipment provided in the central lab manual. Detailed descriptions of the assays will be included in the Bioanalytical Data Reports.

7.14.2. Immunogenicity (IG)

The IG samples will be collected at the timepoints defined in the Assessment schedule (Table 9).

Follow instructions outlined in the Central Laboratory Manual regarding sample collection, numbering, processing, and shipment. See Section 7.15 regarding the potential use of residual samples.

Immunogenicity analytical method(s)

A ligand-binding assay will be used to detect anti-MAA868 antibodies. The analytical method will be described in detail in the IG Bioanalytical Data Report.

7.15. Use of residual biological samples

Residual blood samples may be used for another protocol specified endpoint.

Any residual samples remaining after the protocol-defined analysis has been performed may be used for additional exploratory analysis. This may include but is not limited to using residual samples for protein binding, metabolite profiling, biomarkers of transporters or metabolic enzyme activity (such as 4-beta-hydroxycholesterol levels) or other bioanalytical purposes (e.g. cross check between different sites and/or stability assessment). Given the exploratory nature of the work, the analytical method used for those assessments may not be validated. As such, the results from this exploratory analysis will not be included in the clinical study report.

8. SAMPLE SIZE AND DATA ANALYSES

8.1. Determination of Sample Size

A sample size of 16 subjects per treatment dose cohort with a ratio of 3:1 for MAA868 and placebo treatment assignment is based on historic data considerations. For example, if the observed proportion of patients in a cohort achieving target levels of inhibition is 11/12, the 90% confidence interval would be 0.66 to 0.996.

8.2. Analysis Populations

All Randomized Set will include all subjects who are randomized

Full Analysis Set will include randomized subjects excluding those subjects who are randomized into the study in error and did not receive study drug. Subjects will be analyzed based on the assigned treatment at the randomization.

Per Protocol Set will include subjects in Full Analysis Set and those subjects have no major protocol deviation after randomization.

Safety Set will include randomized subjects who at least received one dose of study drug. Subjects will be analyzed based on the actual treatment taken.

PK/PD Analysis Set will comprise all subjects who received at least one dose of study drug and have at least one PK/PD assessment. Subjects will be analyzed based on the actual treatment taken.

8.3. General Considerations

All efficacy analysis will be based on the Full Analysis Set or Per Protocol Set and will be performed based on the assigned treatment arm at the randomization. Only descriptive statistics will be summarized, no statistical inference will be calculated in efficacy.

Safety analysis will be performed using Safety Set. Subjects will be analyzed based on the actual treatment taken.

PK and PD analysis will be based on PK/PD Analysis Set.

Continuous variables will be summarized by number of subjects [n], mean, standard deviation [SD], median, minimum [min], and maximum [max]. Categorical variable will be summarized using frequency [N] and percentage [%].

8.4. Demographics and Baseline characteristics

All baseline summaries will be based on the All Randomized Set and Full Analysis Set populations.

Gender, race and ethnicity will be summarized using counts and percentages. Age, height (cm), and weight (kg) will be summarized with descriptive statistics (number of subjects [n], mean, SD, median, minimum [min], and maximum [max]). Age may be summarized by decades using N and %.

The listing of subjects with abnormal physical examination findings at screening will be presented. The number and percent of subjects with medical history events will be summarized. Vital signs

collected at screening (sitting diastolic and systolic blood pressure, pulse, temperature and body weight) will be summarized with descriptive statistics (n, mean, SD, median, min, and max).

8.5. Efficacy Analysis

8.5.1. Primary Efficacy Outcome Measures

Within each treatment cohort patients will be randomized 3:1 to active drug or placebo.

The primary analysis variable is whether a subject will achieve a certain percentage FXI inhibition at trough (Day 91). The response rate per treatment group will be calculated by number of subjects who achieve targeted FXI inhibition rate divided by the total number of subjects in the treatment group. The dose regimens and targeted FXI inhibition achievement for Cohorts 1 and 2 are as follows

Cohort 1 (MAA868 120 mg monthly or placebo): Targeted to achieve ≥ 50% FXI inhibition in 90% of subjects at trough (Day 91).

Cohort 2 (MAA868 180 mg monthly or placebo): Targeted to achieve ≥ 90% FXI inhibition in 90% of subjects at trough (Day 91).

The "on treatment" trough FXI levels will be used for the primary analysis, where "on treatment" FXI level is defined as a value which is collected within 30 (±5) days after the last administration of MAA868. The estimate of the responder rate (%) at Day 91 will be presented for each dose regimens of MAA868 together with 2-sided 90% confidence intervals (CI) computed via the Clopper-Pearson exact binomial method.

8.5.2. Secondary Efficacy Outcome Measures

The secondary efficacy analysis is to evaluate the proportion of subjects achieving FXI inhibition ≥ 50%, ≥80%, and ≥90% at trough after the first and second dose (Day 31 and Day 61) at 3 dose levels of MAA868. The analyses described for the primary endpoint will be repeated for the secondary efficacy variables as follows:

- Cohort 1 (MAA868 120 mg monthly or placebo): at Day 31 and 61.
- Cohort 2 (MAA868 180 mg monthly or placebo): at Day 31 and 61
- Cohort 3 (MAA868 TBD mg monthly or placebo): at Day 31 and 61

8.6. Safety Analysis

The safety evaluation includes the analysis of bleeding events, AEs, major cardiovascular, cerebrovascular, systemic arterial, and venous thromboembolism events, laboratory data, ECG, vital signs, hypersensitivity reactions, injection site reactions, and development of anti-drug antibodies. All safety analysis will be performed using the Safety Set.

8.6.1. Adverse Events

The Investigator's verbatim term of each AE will be mapped to system organ class (SOC) and preferred term (PT) using the MedDRA dictionary.

Treatment-emergent Adverse Events (TEAEs) will be of primary interest. The TEAEs will be summarized by SOC and PT; a subject will only be counted once per SOC and once per PT within a treatment. If a subject reports more than one AE with the same PT, the AE with the maximum severity will be presented. Subject counts and percentages and event counts will be presented for each treatment and totaled for all treatments for the following summaries:

- All TEAEs
- Serious TEAEs
- All TEAEs by severity
- All TEAEs by relationship to study drug
- TEAEs potentially related to study drug
- TEAEs potentially related to study drug by severity
- TEAEs leading to discontinuation of study drug
- TEAEs leading to withdrawal from the study

Adverse events of special interest (AESI) will be reported for a selection of interested AE terms that are specific to Sponsor's product and program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor can be appropriate.

The AESIs for this study are defined as follows:

1. TERM 1
2. TERM 2

Similarly, to the TEAE summary, the AESI will be summarized in the following:

1. All AESIs
2. Serious AESIs
3. All AESIs by severity
4. All AESIs by relationship to study drug
5. AESIs leading to discontinuation of study drug
6. AESIs leading to withdrawal from the study

No statistical inference between the treatments will be performed on AEs.

Listings will be presented by subject for all TEAEs, AESIs, as well as for SAEs, TEAEs associated with outcome of death, and TEAEs leading to discontinuation from the study.

8.6.2. Bleeding Events

An analysis will be performed for the composite safety endpoint of major and CRNM bleeding events which occur on-treatment from the first dose of the study drug to the last dose of the study drug + 30 days if the subject permanently discontinues the study drug prior to the third dose on Day 91. The number of events and the incidence of adjudicated bleeding events will be tabulated

based on ISTH definition by treatment including the composite endpoint of major bleeding events and/or CRNM bleedings.

Major bleeding events (Yes/No)

CRNM bleeding events (Yes/No)

Total bleeding events (Yes/No)

If a subject has more than one bleeding event in each above category, the subject will be counted only once in the tabulation.

The adjudicated outcome will be the basis for any interim and final analysis.

8.6.3. Major cardiovascular, cerebrovascular, and venous thromboembolic events

An analysis will be performed for the composite safety endpoint of major cardiovascular, cerebrovascular, and venous thromboembolic events which occur on-treatment from the first dose of the study drug to the last dose of the study drug + 30 days if the subject permanently discontinues the study drug prior to the third dose on Day 91.

The number of events and the incidence of adjudicated events will be tabulated based on the outcomes adjudicated by experienced medical personnel, and the adjudicated outcome will be the basis for any interim and final analysis.

8.6.4. Clinical Laboratory Evaluations

Clinical laboratory results in continuous values at each timepoint and for change from baseline will be displayed using summary statistics (n, mean, median, SD, minimum and maximum values).

A laboratory value that is within the central laboratory's reference range will be considered normal. A laboratory value that is outside the central laboratory's normal range will be considered abnormal and will be flagged as either high (H) or low (L). The number and percentage of subjects with abnormal laboratory values will be summarized for each scheduled visit. In addition, shift tables will be presented to display the shift in the normal range categories (L, normal [N], H) from baseline to specified timepoint. Laboratory results in clinical significance will also be summarized in tabulation.

All clinical laboratory data will be presented in listings. Baseline is defined as the result obtained prior to first administration of study medication. Laboratory data will be summarized in SI units.

8.6.5. Vital Sign Measurements

Pre-dose values, post-dose values, and the change from baseline in vital sign measurements (sitting diastolic and systolic blood pressure, pulse, temperature and body weight) will be summarized with descriptive statistics (n, mean, SD, median, min, and max) at each timepoint by treatment. The baseline value will be value just prior to first administration of study medication.

8.6.6. ECG Parameters

The ECG measures (QTc-B, QTc-F, QT, RR, ventricular rate, PR, and QRS) will be listed and summarized with descriptive statistics (n, mean, SD, median, min, and max) at each timepoint by treatment.

The listings of subjects with abnormal ECG results, as judged by the Investigator, will be displayed and will be calculated. The baseline will be the value just prior to first administration of study medication.

8.7. Pharmacokinetic Analysis

Descriptive summary statistics will be provided by treatment and visit/sampling timepoint with descriptive statistics (n, mean, SD, median, min, and max) at each timepoint by treatment. An exception to this is T_{max} where median, minimum and maximum will be presented.

Concentrations below the lower limit of quantitation (LLOQ) will be treated as zero in summary statistics and for PK parameter calculations. A geometric mean will not be reported if the dataset includes zero values.

Individual total MAA868 plasma concentration data will be listed by treatment (MAA868 arms only), subject, and visit/sampling timepoint. PK parameters will also be listed by treatment and subject.

8.8. Biomarkers

Coagulation parameters, including free and total FXI, FXI:C, and immunogenicity will be summarized by timepoint and treatment.

8.9. Interim Analysis

Safety and tolerability data (AEs, laboratory assessments, vital signs and ECG data) will be evaluated from Cohort 1 by the Sponsor's Medical Monitor and Covance Lead Project Physician after approximately 10 of the patients in cohort 1 have received their second dose of study drug and have been followed for at least an additional 14 days. The decision to proceed to cohort 2 will be made only after it is confirmed that the cohort 1 dose was safe and tolerated and all planned subjects in cohort 1 have been randomized. If notable AEs or safety concerns are found in cohort 1, the study may be terminated.

Likewise, after approximately 10 of the patients in cohort 2 have received their second dose of study drug and have been followed for at least an additional 14 days, safety, tolerability, and other analyses will be evaluated.

Additional IAs may be conducted to support decision making concerning the current clinical study, the Sponsor’s clinical development projects in general or in case of any emergent safety concerns. The Investigator(s) may be included for decisions with regards to any unplanned IAs that address questions of subject safety.

Unblinded IA results will be reviewed by the Sponsor (or their designees).

No further dissemination of interim results should occur, in particular not with individuals involved in treating the study’s subjects or assessing clinical data (e.g. ECGs, symptoms) obtained in the study.

8.10. Data Quality Assurance

Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Covance representative will review the protocol and CRFs with the Investigator(s) and their staff. During the study Covance employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The monitor will visit the site to check the completeness of subject records, the accuracy of entries on the CRFs, the adherence to the protocol and to GCP, the progress of enrollment, and ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits.

The Investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The Investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Covance monitoring standards require full verification for the presence of informed consent, adherence to the eligibility criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

Data collection

Designated Investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the electronic data capture (EDC) system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to Covance working on behalf of Anthos. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the Investigator will receive copies of the subject data for archiving at the investigational site.

Data not requiring a separate written record are noted on the Assessment schedule (Table 9) and can be recorded directly on the CRF. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

Database management and quality control

Covance will review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. Site personnel will complete and sign the faxed copy and fax it back to Covance who will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally, and the results will be sent electronically to Covance.

At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Covance.

The occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked, and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Anthos Head of Regulatory and the Chief Medical Officer.

9. ETHICAL CONSIDERATIONS

9.1. Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

9.2. Responsibilities of the Investigator and IRB

Before initiating a trial, the Investigator/institution must obtain approval/favorable opinion from the IRB for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Covance monitors, auditors, Covance Quality Assurance representatives, designated agents of Anthos, IRBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the Investigator must inform Anthos immediately that this request has been made.

For multi-center trials, a Coordinating Investigator will be selected by Anthos around the time of Last Patient Last Visit to be a reviewer and signatory for the CSR.

9.3. Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. Upon study completion and finalization of the study report the results of this trial will be posted in a publicly accessible database of clinical trial results in accordance with local regulations.

No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement between the Sponsor and the investigator and/or the investigator's institution.

The information developed from this clinical study will be used by the Sponsor in connection with the development of MAA868 and other drugs and diagnostics, and thus may be disclosed as required to other clinical investigators, business partners, or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the Sponsor with all data obtained in the study.

10. PROTOCOL ADHERENCE

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances is an Investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an Investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Anthos and approved by the IRB and health authorities, where required, it cannot be implemented.

10.1. Protocol Amendments

Any change to the protocol can only be made in a written protocol amendment that must be approved by Anthos, Health Authorities where required, and the IRB prior to implementation.

Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB is notified.

Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7.6.2 (Safety Monitoring) must be followed and the Study Lead informed.

11. REFERENCES

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12. APPENDICES

12.1. Appendix 1 - Liver Event Definitions and Follow-up Requirements

Table 4: Liver Event Definition

Definition	Thresholds
Potential Hy's law cases	• ALT or AST > 3 X ULN and TBL > 2 × ULN without initial increase in ALP to > 2 × ULN
ALT or AST elevation with coagulopathy	• ALT or AST > 3 × ULN and INR > 1.5 (in the absence of anticoagulation)
ALT or AST elevation accompanied by symptoms	• ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash, or eosinophilia
Isolated ALT or AST elevation	• ALT or AST > 8 × ULN • 5 x ULN < ALT/AST ≤ 8 x ULN • 3 x ULN ALT/AST 5 x ULN
Isolated ALP elevation	• ALP > 2 × ULN (in the absence of known bone pathology)
Others	• Any clinical event of jaundice (or equivalent term) Any adverse event potentially indicative of liver toxicity

Table 5: Action required for Liver Events

Criteria	Action required
Potential Hy's law cases ALT or AST elevation with coagulopathy ALT or AST elevation accompanied by symptoms Isolated ALT or AST elevation > 8 X ULN Jaundice	• Hospitalize, if clinically appropriate • Establish causality • Complete CRFs per liver event guidance
Isolated ALT or AST elevation > 5 to ≤ 8 X ULN	• Establish causality • Complete CRFs per liver event guidance
Isolated ALT or AST elevation > 3 to ≤ 5 × ULN (patient is asymptomatic)	• Monitor liver chemistry tests two or three times weekly
Isolated ALP elevation	• Repeat liver chemistry tests within 48-72 hours • If elevation is confirmed, measure fractionated ALP; if >50% is of liver origin, establish hepatic causality • Complete CRFs per liver event guidance
Any AE potentially indicative of liver toxicity	• Hospitalize if clinically appropriate • Complete CRFs per liver event guidance

Table 6: Exclusion of underlying Liver Disease

Disease	Assessment
Hepatitis A, B, C, E	• IgM anti-HAV; HBSAg, IgM anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	• ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	• Ethanol history, γGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	• Ultrasound or MRI
Hypoxic/ischemic hepatopathy	• Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI
Biliary tract disease	• Ultrasound or MRI, ERCP as appropriate
Wilson disease	• Caeruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-anitrypsin

12.2. Appendix 2 - Specific Renal Alert Criteria and Actions

Table 7: Specific Renal Alert Criteria and Actions

Criteria	Action required
Serum creatinine (sCr) increase 25 – 49% compared to baseline	• Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase ≥ 50%	• Consider causes and possible interventions • Repeat assessment within 24-48 hours if possible • Consider hospitalization and specialized treatment
Protein-creatinine or albumin-creatinine ratio increase ≥ 2-fold, or new onset dipstick proteinuria ≥ 1+ , or Albumin-creatinine ratio (ACR) ≥ 30 mg/g or ≥ 3 mg/mmol, or Protein-creatinine ratio (PCR) ≥ 150 mg/g or >15 mg/mmol	• Consider causes and possible interventions • Assess serum albumin and serum protein • Repeat assessment to confirm
New onset glucosuria on urine dipstick (unless related to concomitant treatment, diabetes)	<u>Assess and document:</u> • Blood glucose (fasting) • Serum creatinine • Urine albumin-creatinine ratio
New hematuria on dipstick	<u>Assess and document</u> • Urine sediment microscopy • Assess sCr and urine albumin-creatinine ratio • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

Additional specialized assessments are available to assess renal function or renal pathology.
(Note: In exceptional cases when a nephrologist considers a renal biopsy, it is strongly recommended to make specimen slides available for evaluation by Anthos to potentially identify project-wide patterns of nephrotoxicity.)
Whenever a renal event is identified, a detailed subject history and examination are indicated to identify, document and potentially eliminate risk factors that may have initiated or contributed to the event:

- Blood pressure assessment (after 5 min rest, with an appropriate cuff size)
- Signs and symptoms such as fever, headache, shortness of breath, back or abdominal pain, dysuria, hematuria, dependent or periorbital edema
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output
- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other potential causes of renal dysfunction, e.g., dehydration, hemorrhage, tumor lysis

Table 8: Follow-up renal events

Action	Follow up
Assess*, document and record in the CRF or via electronic data load. Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc.) in the CRF	• Urine dipstick and sediment microscopy • Blood pressure and body weight • Serum creatinine, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate, and uric acid • Urine output
Monitor subject regularly (frequency at Investigator's discretion) until:	• Event resolution: (sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline) OR • Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.

*Urine osmolality: in the absence of diuretics or chronic kidney disease this can be a very sensitive metric for integrated kidney function that requires excellent tubular function. A high urinary osmolality in the setting of an increase in sCr will point toward a "pre-renal" cause rather than tubular toxicity.

12.3. Appendix 3 - Clinical notable laboratory values

Clinical notable laboratory values:

The definition, the specific alert criteria and the corresponding actions for hepatic and renal notable laboratory abnormalities are respectively provided in Appendix 1 and Appendix 2.

The following laboratory values are considered clinically notable and should be forwarded to Covance at the same time that they are sent to Investigators:

- A change from baseline in hemoglobin ≥ 2 g/dL
- A decrease from baseline in platelets count ≥ 50% or < 100 x 10^9/L
- A positive fecal occult blood test
- Macroscopic hematuria

Whenever a clinically notable laboratory value is identified, a detailed subject history and examination are indicated to identify, document and potentially eliminate a bleeding event:

- Blood pressure assessment (after 5 min rest, with an appropriate cuff size);
- Signs and symptoms such as shortness of breath, tiredness, abdominal pain, hematemesis, rectorrhagia, melena, gingival or nose bleeding, bruising and hematoma;
- Concomitant events or procedures such as trauma, surgical procedures.

When one of the above occurs the action plan is as follows:

- Confirm the value, assess and document the clinically notable laboratory value in the CRF or via electronic data load;
- Investigate the underlying causes such as clinical or subclinical bleeding event and the contributing factors such as intake of prohibited medications;
- Monitor subject regularly (frequency at Investigator's discretion) until resolution or stabilization. Hospital admission, additional laboratory tests, endoscopy, volume replacement, transfusion, etc. should be performed at the Investigator's discretion and according to the medical needs (see Section 6.3 for reversal therapy).

12.4. Appendix 4 - Schedule of Assessments

Table 9: Schedule of Assessments

Period	Screening	Treatment							Washout / Follow-up			
Visit	1	2	3	4	5	6	7	8	9	10	TD	EoS
Day	-28 to -3	1 (predose)	11	31 (predose)	41	61 (predose)	71	91	101	121	-	170
Window			±2	±2	±3	±2	±3	±2	±3	±3		±10
Informed consent	X											
Medical history	X											
Drug & alcohol screen	X											
I/E criteria	X	X										
Physical Exam	X	X	X	X		X		X		X	X	X
Height	X											
Weight	X	X										X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X						X				X
HIV, Hepatitis B, Hepatitis C	X											
aPTT, Free and total FXI	X	X	X	X	X	X	X	X	X	X	X	X
aPTT (corrected for FXI), FXI:C		X				X		X				X
PK assessment: total MAA868		X	X	X	X	X	X	X	X	X		X
Antidrug antibodies (ADA)		X		X		X	X	X		X		X
Exploratory biomarker collection	X	X		X		X		X		X		
Complete safety Labs	X	X	X	X	X	X		X		X	X	X
Pregnancy test	Serum	Urine			Urine			Urine			Urine	Urine
Urine dipstick	X	X	X	X	X	X		X		X	X	X
Fecal occult blood test	X	X										
AE collection	X											
Concomitant meds	X											
Local assessment of CV and cerebrovascular events		X										
Local assessment of bleeding events		X										
Dispense Study Medications		X		X		X						
Drug Accountability		X		X		X		X				
MAA868		X		X		X						
Placebo		X		X		X						

Period	Screening	Treatment							Washout / Follow-up			
Visit	1	2	3	4	5	6	7	8	9	10	TD	EoS
Day	-28 to -3	1 (predose)	11	31 (predose)	41	61 (predose)	71	91	101	121	-	170
Window			±2	±2	±3	±2	±3	±2	±3	±3		±10
Injection site inspection (post-dose)		X	X	X	X	X	X					
Study disposition								X			X	X
TD = Study treatment discontinuation; EoS = End of Study; FXI:C = Factor XI coagulation activity												

ANTHOS THERAPEUTICS, INC.

MAA868

Clinical Trial Protocol ANT-004

A Multicenter, Randomized, Subject- and Investigator-blinded, Placebo-controlled, Parallel-group, Dose-range Finding Study to Assess the Pharmacokinetic and Pharmacodynamic Parameters, Safety, Tolerability, and Immunogenicity of MAA868 in Patients with Atrial Fibrillation

Document type:	Protocol
IND number:	129008
EUDRACT number:	N/A
Version number:	V01 - Initial Protocol
Clinical Trial Phase:	IIa
Release date:	27-September-2019
Sponsor:	Anthos Therapeutics 55 Cambridge Pkwy, Ste. 103 Cambridge, MA 02142 Tel: 617-430-6940
Chief Medical Officer (CMO)	[redacted]

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Protocol Number: ANT-004

Protocol Title: A Multicenter, Randomized, Subject- and Investigator-blinded, Placebo-controlled, Parallel group, Dose-range Finding Study to Assess the Pharmacokinetic and Pharmacodynamic Parameters, Safety, Tolerability, and Immunogenicity of MAA868 in Patients with Atrial Fibrillation

Principal Investigator's Statement and Signature:

I, the undersigned, have read protocol ANT-004 (including all appendices). I agree to conduct the clinical study as described and in compliance with International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements. I agree to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____ _____

Signature of Principal Investigator **Date**

_____

Name of Principal Investigator (printed)

Investigative Site Name, Address and Telephone Number:

_____

_____

_____

_____

Sponsor CMO Signature

CMO Approval: _____

Date: _____

NOTIFICATION OF SERIOUS ADVERSE EVENTS

Dear Investigator,

You must report a serious adverse event (SAE) (initial or follow-up) to Covance as summarized below. Refer to Section 7.6.2 of the protocol for SAE criteria and additional requirements. See also the Safety Management Plan for further details on the method of reporting a SAE.

- Complete SAE report
- Submit SAE report to Covance safety within 24 hours after awareness of the SAE
- Notify the Covance Medical Lead
- The fax number(s) and email address(es) are located in the Safety Management Plan.

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LIST OF ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
AESI	Adverse event of special interest
AF	Atrial fibrillation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CK	creatine kinase
CI	confidence interval
CRF	case report form
CRNM	clinically relevant non-major
CRO	contract research organization
CSR	clinical study report
DOAC	direct oral anticoagulant
DSS	Drug Safety Services
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
FDA	Food and Drug Administration
FIH	first-in-human
FXI	Factor XI
FXI:C	FXI coagulation activity
GCP	Good Clinical Practice
γGT	gamma glutamyl transferase
GLP	Good Laboratory Practice
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
IRB	institutional review board

IN	investigator notification
MedDRA	Medical Dictionary for Regulatory Activities
PAF	paroxysmal atrial fibrillation
PD	pharmacodynamic
PK	pharmacokinetic
QTcF	QT interval corrected by Fridericia formula
RBC	red blood cells
SAE	serious adverse event
SAP	statistical analysis plan
s.c.	subcutaneous
sCr	serum creatinine
sCT	spiral computed tomography
SD	standard deviation
SOC	system organ class (MedDRA classification)
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
VTE	venous thromboembolism
WBC	white blood cells

PHARMACOKINETIC DEFINITIONS AND SYMBOLS

AUC_{0-t}	The area under the plasma concentration-time curve from time zero to time 't' where t is a defined time point after administration [mass x time / volume]
AUC_{inf}	The area under the plasma concentration-time curve from time zero to infinity [mass x time / volume]
AUC_{last}	The area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration [mass x time / volume]
C_0	The initial concentration at the end of an intravenous infusion
CL	The systemic clearance following intravenous administration
C_{max}	The observed maximum plasma concentration following subcutaneous drug administration [mass / volume]
F	Bioavailability
$T_{1/2}$	The terminal elimination half-life [time]
T_{max}	The time to reach the maximum concentration after drug administration [time]
Vss	The steady state volume of distribution following intravenous administration

GLOSSARY OF TERMS

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Dosage	Dose of the study treatment given to the subject in a time unit
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with "investigational new drug" or "test substance"
Screen Failure	A subject who is screened but is not treated or randomized
Subject	A trial participant
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Study treatment period	Interval of time in the planned conduct of a study. A treatment period is associated with a purpose (e.g. screening, randomization, treatment, follow-up), which applies across all arms of a study
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent	Withdrawal of consent from the study is defined as when a subject does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

PROTOCOL SYNOPSIS

Title of study: A Multicenter, Randomized, Subject- and Investigator-blinded, Placebo-controlled, Parallel-group, Dose-range Finding Study to Assess the Pharmacokinetic and Pharmacodynamic Parameters, Safety, Tolerability, and Immunogenicity of MAA868 in Patients with Atrial Fibrillation

Indication: Atrial fibrillation

Number of Investigators and study centers:
The study is planned to be conducted in approximately 6 sites.

Development phase: Phase 2a

Objectives:
Primary
- To evaluate the proportion of patients that achieve ≥50%, ≥80%, or ≥90% Factor XI (FXI) inhibition at trough after the third dose (Day 91) at different dose levels of MAA868.

Secondary
- To evaluate the proportion of patients achieving FXI inhibition ≥ 50%, ≥80%, and ≥90% at trough after the first and second dose (Day 31 and Day 61) at different dose levels of MAA868.
- To evaluate the safety and tolerability following multiple s.c. administration of MAA868 compared to placebo to patients with AF.
- To evaluate the incidence of major bleeding events, clinically relevant non-major (CRNM) bleeding events and total bleeding with MAA868 relative to placebo during the treatment period.
- To evaluate the immunogenicity of MAA868 compared to placebo.

Study design:
This is a randomized, subject- and investigator-blinded, placebo controlled, dose-ranging study in patients with atrial fibrillation (AF) or atrial flutter who are at low risk for stroke. Patients will be enrolled in up to 3 cohorts of approximately 16 patients each. After a Screening Period of up to 4 weeks, patients in will be randomized in a 3:1 ratio (MAA868:placebo) to receive 3 monthly subcutaneous (s.c.) injections and followed for pharmacokinetics, pharmacodynamic efficacy as well as safety events over the 90-day Treatment Period. Patients will then be followed up to Day 170 during the Washout/Follow-up period.

Number of patients:
Approximately 48 patients will be randomized into the study.

Diagnosis and main criteria for inclusion and exclusion:
Inclusion Criteria
- Male and female patients ≥ 18 and < 85 years old
- Current AF or atrial flutter on 12 lead electrocardiography at Screening
  or
  a history of paroxysmal AF (PAF) or atrial flutter as documented by prior telemetry, 12 lead electrocardiography or ambulatory (e.g. Holter or patch) monitor which is not due to a reversible condition (e.g. alcohol binge drinking)
- A CHA2DS2-VASc risk score of 0-1 for men and 1-2 for women and in whom, in the investigator's judgment, the use of an anticoagulant for stroke prevention is not indicated
- Body weight between 50 and 130 kg, inclusive

Exclusion criteria

- History of stroke, transient ischemic attack or systemic embolism
- History of major bleeding during treatment with an anticoagulant or antiplatelet therapy. (Patients who have had major bleeding on anticoagulants or antiplatelet therapy more than a year ago can be enrolled only if the bleeding was due to a reversible cause, e.g. gastro-duodenal ulcer, that was successfully treated)
- History of traumatic or non-traumatic intracranial, intraspinal or intraocular bleeding.
- Known bleeding diathesis or any known active bleeding at screening or baseline
- Family history of bleeding disorder
- Known active GI lesions predisposing to bleeding events
- Myocardial infarction, unstable angina pectoris or coronary artery bypass graft (CABG) surgery within 12 months prior to the screening period
- Clinically significant moderate or greater mitral stenosis severity (valve area <1.5 cm^2)
- Prosthetic heart valve
- Uncontrolled hypertension defined as SBP/DBP ≥ 160/100 mmHg at the screening visit
- NYHA class III-IV heart failure
- Currently being treated with anticoagulant therapy or have been on anticoagulants in the previous 12 months. Potential patients who have been on anticoagulation more than 12 months ago requires discussion with the sponsor before enrolling.
- Currently being treated with antiplatelet therapy such as a P2Y12 inhibitor or aspirin. Low dose aspirin (≤ 100 mg/d) is allowed
- Severe renal impairment as defined as an estimated glomerular filtration rate ≤45 mL/min/1.73m^2 by the MDRD equation at the screening visit
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception

Test products, dose, and mode of administration:
MAA868 with a dose of 120 mg or 180 mg or placebo s.c. monthly

Reference therapy, dose, dose form, and mode of administration:
Matching placebo to MAA868 s.c. monthly

Duration of patient participation in study:
Planned Screening duration: Up to 4 weeks
Planned treatment duration: Day 0-91: 91 days
Planned follow-up duration: Day 91 to Day 170: 79 days

Study populations:
Approximately 48 male and female patients age ≥ 18 to < 85 with AF or flutter, as defined above, will be randomized into the study.

Evaluation: Efficacy
- Free FXI concentrations at Days 31, 61 and 91

Evaluation: Safety
- Confirmed major bleeding events, clinically relevant non-major (CRNM) bleeding events and total bleeding events
- Adverse and serious adverse events
- Occurrence of major cardiovascular, cerebrovascular, systemic arterial, and
- Physical examinations
- Monitoring of laboratory parameters in blood
- ECGs
- Hypersensitivity reactions
- Injection site reactions

Evaluation: Other assessments
- Factor XI coagulation activity
- Activated partial thromboplastin time
- Pharmacokinetics
- Development of anti-drug antibodies
- Venous thromboembolic events

Statistical methods:
The patients will be enrolled into cohorts of approximately 16 patients with each cohort evaluating a different dose level of MAA868. Within each cohort, patients will be randomized 3:1 to active drug or placebo.
The primary analysis variable is whether a subject will achieve pre-defined degrees of FXI inhibition at trough (Day 91). The dose regimens and targeted FXI inhibition achievement are as follows:
Low-dose cohort (MAA868 120 mg monthly or placebo): Targeted to achieve ≥ 50% FXI inhibition in 90% of subjects at trough (Day 91).
High dose cohort (MAA868 180 mg monthly or placebo): Targeted to achieve ≥ 90% FXI inhibition in 90% of subjects at trough (Day 91).
The "on treatment" trough FXI levels will be used for the primary analysis, where "on treatment" FXI level is defined as a value which is collected within 30 (±5) days after the last administration of MAA868. The response rate per treatment group will be calculated by number of subjects who achieve targeted FXI inhibition rate divided by the total number of subjects in the treatment group. The estimate of the responder rate (%) at Day 91 will be presented for each dose regimens of MAA868 together with 2-sided 90% confidence intervals.
The secondary efficacy analysis is to evaluate the proportion of subjects achieving FXI inhibition ≥ 50%, ≥80%, and ≥90% at trough after the first and second dose (Day 31 and Day 61) at multiple dose levels of MAA868. The analyses described for the primary endpoint will be repeated for the secondary efficacy variables.
Safety data including adverse events (AEs), bleeding events, ECG, vital signs, thromboembolic events and laboratory results will be reported by count and incidence rate.

1. INTRODUCTION

1.1. Background

AF is the most common cardiac arrhythmia, accounting for approximately one third of hospitalizations for cardiac dysrhythmias. Currently, it is estimated to affect more than 6 million patients in Europe and approximately 2.3 million in the United States, and this number continues to grow rapidly because of the increasing proportion of the aging population with associated co-morbidities. As such, the prevalence of AF is expected to increase 2- to 3-fold over the following 3 decades in western populations (Kannel and Benjamin 2008).

AF is associated with a 4- to 5-fold increase in embolic stroke. The risk for stroke associated with AF increases steeply with age to 23.5% for patients aged 80 to 89 years (Kannel and Benjamin 2008). Most patients with AF require life-long anticoagulation therapy to prevent cardioembolic stroke and systemic embolism. It is estimated that 85 to 90% of AF patients will require anticoagulation therapy (Camm et al 2012).

Vitamin K antagonists (VKA), such as warfarin, are effective in reducing stroke and systemic thromboembolism; a highly significant relative risk reduction in stroke incidence by 67% was observed in a meta-analysis combining six studies (Hart et al 1999). All-cause mortality was reduced (26%) significantly by VKA vs. control (Hart et al 1999). In recent years, direct oral anticoagulant (DOACs) medications have been approved and introduced to clinical practice. These drugs are at least as effective as warfarin in preventing stroke or systemic embolism and may be superior to warfarin in the risk of hemorrhagic stroke and intracranial hemorrhage (Connolly et al 2009, Granger et al 2011, Patel et al 2011). The incidence of major bleeding events with DOACs was similar or slightly lower than the incidence observed with well-conducted warfarin therapy. Nonetheless, the overall bleeding risk continues to be high with the use of DOACs. For instance, the annual incidence of major and clinically relevant non-major (CRNM) bleeding was 14.9% and the annual incidence of major bleeding events was 3.6% in patients treated with rivaroxaban in the ROCKET AF study (Patel et al 2011). It is notable that the occurrence of major bleeding was strongly associated with mortality. In the same study, the rate of all-cause mortality over the 2-month period following a major bleeding event was 20.4% in the rivaroxaban group and 26.1% in the warfarin group (Piccini et al 2014). Thus, there is a high unmet medical need for an anticoagulant therapy that can effectively reduce the risk of AF-related thromboembolic complications such as stroke but with a lower risk of bleeding than currently employed anticoagulants.

FXI is an emerging target for potentially safer and more effective anticoagulant medications. FXI holds important roles in both the intrinsic and extrinsic coagulation pathways and in bridging the initiation and amplification phases of plasmatic hemostasis (Gailani and Renné 2007). Both Factor XII and thrombin can activate FXI, resulting in a sustained thrombin generation and fibrinolysis inhibition. FXI plays a minor role in normal hemostasis in a high tissue factor environment “after vessel injury” whereas it appears to play a key role in thrombosis. Severe FXI deficiency is associated with a lower incidence of ischemic stroke and venous thromboembolic events (Salomon et al 2008, Salomon et al 2011, Preis et al 2017). Nevertheless, bleeding manifestations in subjects with severe FXI deficiency are infrequent and usually mild. Bleeding events that occur are typically injury-related and preferentially affect tissues known to have increased fibrinolytic

activity such as the oral and nasal mucosa, and urinary tract (Bolton-Maggs 2000). Bleeding in vital organs is extremely rare or non-existent.

MAA868

MAA868 is a human antibody that binds to the catalytic domain of FXI. MAA868 binds to both the zymogen (FXI) and activated factor XI (FXIa) with high potency. MAA868 dose-dependently prolonged activated partial thromboplastin time (aPTT) in in-vitro and in-vivo studies. After a single subcutaneous (s.c.) administration of MAA868 at a 3 mg/kg dose, sustained anticoagulant activity lasting for more than one month was observed in cynomolgus monkeys. Moreover, MAA868 prevented experimental carotid artery thrombosis induced by FeCl3 and resulted in a prolongation in aPTT in FXI-/- mice reconstituted with human FXI. No significant toxicity findings were observed in single dose and in the 13-week Good Laboratory Practice (GLP)-compliant toxicity study conducted in cynomolgus monkeys. The highest s.c. dose administered in the 13-week study was defined as no observed adverse effect level NOAEL (100 mg/kg/week s.c.).

MAA868 was evaluated in a first-in-human (FIH) study (CMAA868X2101) to characterize its safety/tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) in healthy subjects following single s.c. administration. In total, 6 cohorts with 10 subjects each (8 MAA868: 2 Placebo) were enrolled. The doses of MAA868 administered in Cohorts 1 to 5 ranged from 5 mg to 240 mg. In a sixth cohort, 240 mg of MAA868 was administered to subjects with body mass index (BMI $\geq$ 35 kg/m2).

In the FIH study, MAA868 appeared to be safe and well tolerated, and the incidence of AEs were comparable across dose groups and placebo. No bleeding events, hypersensitivity reactions or injection site reactions were reported. Exposure increased with increasing dose of s.c. MAA868; the median maximum observed concentration (C_{max}) occurred on Day 7 to 21 and the mean terminal elimination half-life ranged from 20 to 28 days. A dose and time-dependent prolongation of aPTT occurred with MAA868 after single s.c. administration; the 150 mg dose resulted in a mean aPTT prolongation $\geq$ 2-fold at Day 29. Doses greater than 150 mg extended the duration of aPTT prolongation but did not produce a greater prolongation of aPTT. Robust and sustained reductions of free FXI $\geq$ 90% were observed with 150 mg MAA868 at Day 29 and up to Day 43 with 240 mg. A high BMI was associated with a lower MAA868 exposure and slightly shorter duration of aPTT prolongation. Robust reductions in free FXI and in FXI coagulation activity and relevant aPTT prolongation are predicted to occur within 12 to 24 hours after MAA868 s.c. administration with relevant clinical doses.

MAA868 was also studied in healthy Japanese subjects in a single ascending dose, randomized, subject- and investigator-blinded, placebo-controlled, non-confirmatory study to assess safety, tolerability, PK and PD. Three cohorts (MAA868 dose levels: 15, 50 and 150 mg) were enrolled in this study and received a single s.c. dose of MAA868 or matching placebo (8 subjects received MAA868 and 2 subjects received placebo in each cohort). Assessments and assessment schedules were generally similar to the FIH study. No SAE or study discontinuation due to AEs were reported in this study. All AEs were mild in intensity and the distribution of AEs was well balanced between the MAA868 dose groups and placebo. No bleeding event, hypersensitivity or injection site reactions were reported in the study. PK analysis suggested that there was no indication of an impact of the Japanese ethnicity on exposure or PD parameters of MAA868 in healthy subjects.

Taken together, the results from both completed studies of MAA868 suggest that the administration of MAA868 is safe and well-tolerated. Subcutaneous administration of MAA868 leads to robust and sustained effects on aPTT, free FXI, and FXI coagulation activity (FXI:C) up to/through Day 29 with the 150 mg dose and Day 43 with the 240 mg dose in subjects with normal body weight or class 1 obesity (BMI <35 kg/m2). In subjects with class 2 or 3 obesity (BMI ≥35 kg/m2), exposures of MAA868 may be lower and the duration of aPTT prolongation is shorter.

1.2. Study Rationale

This study is a multicenter, randomized, subject and Investigator-blinded, placebo-controlled, parallel-group, multiple ascending dose-ranging study to evaluate the safety, tolerability, PK, and PD effects of MAA868 in patients with AF or flutter at low risk of thromboembolic stroke or peripheral embolism. The trial will evaluate the effects of up to three different doses of MAA868 on FXI inhibition, indices of coagulation, and thrombogenesis biomarkers compared to placebo. The incidence of injection site reactions, bleeding events, immunogenicity, and systemic arterial and venous thromboembolic events will also be assessed. Results from this study will assist with dose-selection of MAA868 for a phase 3 trial in patients with AF.

1.3. Benefit-risk Assessment

AF is associated with a 4- to 5-fold increase in embolic stroke. MAA868, a fully human monoclonal antibody targeting Factor XI, is being considered for development as a novel anticoagulant for patients with AF or flutter. FXI is an emerging target as a novel anticoagulant. Several lines of evidence suggest that FXI inhibition has the potential to prevent thrombosis with minimal risk of bleeding. For example, individuals with an inherited deficiency of FXI have been reported to have a lower risk of VTE even though their bleeding phenotype is variable and often quite mild. Further support of the safety of inhibiting FXI comes from clinical studies using an investigational FXI antisense oligonucleotide (FXI-ASO) where administration of FXI-ASOs in healthy subjects and in patients undergoing total knee arthroplasty was demonstrated to be safe and well-tolerated (Buller et al 2015).

Results from the first-in-human (FIH) study of MAA868 (CMAA868X2101) demonstrated that a single s.c. administration of MAA868 at increasing doses up to 240 mg in healthy subjects were safe and well-tolerated. These doses of MAA868 resulted in a robust and sustained FXI inhibition and prolongation of aPTT. The safety and pharmacodynamic efficacy of MAA868 was further supported by preliminary data from the study CMAA868A1101, which showed a good safety profile of MAA868 in Japanese heathy male subjects.

This study is designed to evaluate the efficacy and safety of achieving different levels of FXI inhibition with different dose levels of s.c. MAA868 in patients with AF or flutter. This study will recruit patients with AF or flutter who are judged by their physician to be at low risk for stroke based on clinical guidelines. In each case, patients will ***only*** be enrolled if their physician has determined that the patient does not merit anticoagulation based on the guidelines and the physician's assessment of the benefit-risk profile for that patient. The guidelines state that the benefits of anticoagulation in AF patients at low risk of embolic stroke are uncertain given the concomitant risks of bleeding with anticoagulant therapy. Accordingly, the guidelines recommend individualized shared physician-patient decision-making with regards to the decision to initiate anticoagulant therapy in this population (January et al 2019). Patients with PAF will be enrolled who have a CHA2DS2-VASc risk score of 0-1 for men or 1-2 for women, in whom the guidelines

are equivocal regarding the recommendation to initiate anticoagulation and advise an individualized assessment of the benefit-risk of anticoagulation (January et al 2019).

Overall, the nonclinical and clinical data to date support the investigation of MAA868 in the prevention of thromboembolic diseases in patients with AF. The risk-benefit relationship appears to be acceptable.

2. OBJECTIVES AND ENDPOINTS

2.1. Primary objective and endpoint

Objective	Endpoint
• To evaluate the proportion of patients that achieve ≥50%, ≥80%, or ≥90% FXI inhibition at trough after the third dose (Day 91) at different dose levels of MAA868	• Occurrence of achieving ≥50%, ≥80%, or ≥90% inhibition of FXI (<50%, <20%, or <10% free FXI) at trough on Day 91 at different dose levels of MAA868

2.2. Secondary objectives and endpoints

Objective	Endpoint
• To evaluate the proportion of patients achieving FXI inhibition ≥50%, ≥80%, and ≥90% at trough after the first and second dose (Day 31 and Day 61) at different dose levels of MAA868	• Occurrence of achieving ≥50%, ≥ 80%, and ≥90% inhibition of FXI (<50%, <20%, or <10% free FXI) at trough on Day 31 and Day 61 at different dose levels of MAA868
• To evaluate the safety and tolerability following multiple s.c. administration of MAA868 compared to placebo in patients with AF	• All safety endpoints [i.e., physical exam, vital signs, electrocardiogram (ECG), safety laboratories, hypersensitivity reactions, injection site reactions, and adverse events (AEs), including serious AEs (SAEs)] during the Treatment Period and through EoS
• To evaluate the incidence of major bleeding events, clinically relevant non-major (CRNM) bleeding events and total bleeding with MAA868 relative to placebo during the treatment period	• Occurrence of confirmed major bleeding events, CRNM bleeding events and total bleeding events during the treatment period
• To evaluate the immunogenicity of MAA868 compared to placebo.	• Screening and confirmation for anti-drug (MAA868) antibodies (ADA)

2.3. Exploratory objectives and endpoint

Objective	Endpoint
• To evaluate the effect of MAA868 compared to placebo on the incidence of major cardiovascular, cerebrovascular, and venous thromboembolic events (as defined to the right)	• Occurrence of major cardiovascular, cerebrovascular, systemic arterial, and venous thromboembolic events (VTEs)

• To evaluate the change from baseline in D-dimer and other thrombogenesis markers with MAA868 relative to placebo during the treatment period	• Concentrations of D-dimer and other exploratory thrombogenesis markers during the treatment period

3. INVESTIGATION PLAN

3.1. Overall Study Design and Plan Description

This is a phase 2a, randomized, subject- and investigator-blinded, placebo-controlled, multiple ascending dose-ranging study to assess the PK/PD, safety, tolerability, and immunogenicity of MAA868 in patients with AF or flutter.

Patients will be enrolled in at least 2 and up to 3 cohorts of approximately 16 patients each for a total of up to 48 subjects (Figure 1A). Patients in cohort 1 will be randomized 3:1 to receive a 120 mg dose of MAA868 or placebo, respectively on Day 1 with two subsequent monthly injections. After approximately 10 of the patients in cohort 1 have received their second dose of study drug and have been followed for at least an additional 14 days, a safety review of emerging safety and PK data from cohort 1 will take place. Cohort 2 will be initiated after it is confirmed by the Sponsor's Medical Monitor and the Covance Lead Project Physician that the cohort 1 dose was safe and tolerated and all cohort 1 patients have been randomized. Likewise, after 10 of the patients in cohort 2 have received their second dose and have been followed for at least an additional 14 days, interim safety, tolerability, and other analyses will be evaluated by the Sponsor. Based on emerging data, the Sponsor may elect to:

- Enroll cohort 3 to evaluate a higher, lower, or a previously studied dose of MAA868
- Terminate the study

The study is comprised of 3 periods:

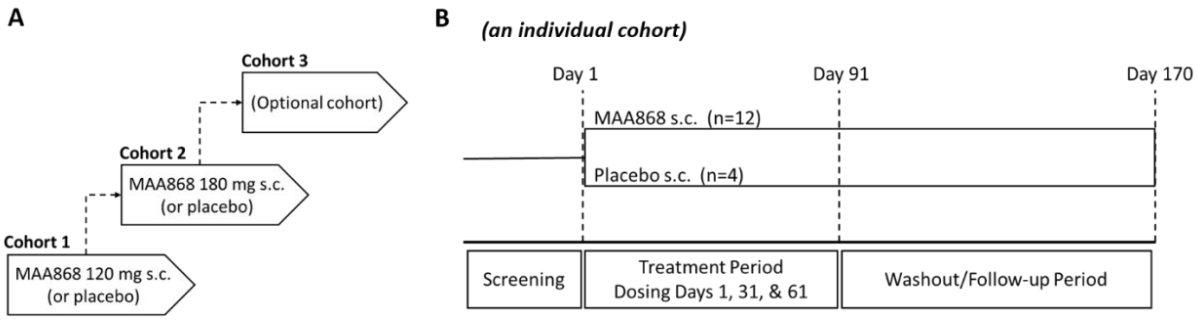
(1) Screening period of up to 4 weeks

(2) Treatment period with MAA868 administered s.c. monthly (or matching placebo) (randomized 3:1) for 90 days

(3) Follow-up period up to end of study (Day 170).

Following the screening period of up to 4 weeks, all patients that meet the study eligibility criteria (Section 4.1 and Section 4.2) will have baseline efficacy and safety assessments performed on Day 1 and then randomized to active or placebo (Figure 1B).

Figure 1: Overall study design



The first dose of study drug will be administered at the study center on Day 1. The second and third doses of study drug will also be administered at the study center to patients on the Day 31 visit and Day 61 visit, respectively.

During the treatment period, patients will return to the study center on Day 11, Day 31, Day 41, Day 61, Day 71, and Day 91 for safety assessments such as vital signs, AE assessments, laboratory tests, PK, PD, thrombogenesis biomarkers, and other study assessments according to the assessment schedule shown in Table 9.

During the follow-up period, patients will continue to be followed for PK, PD, thrombogenesis, and other study assessments. Patients will return to the study center on Day 101, Day 121 and Day 170 (end of study; EoS) for the evaluations described in the assessment schedule (Table 9).

3.2. Discussion of Study Design, Including the Choice of Control Groups

Rationale for route of administration and treatment duration. The s.c. route of administration was chosen because it is the route of administration anticipated for subsequent studies in patients with AF. In the FIH study of MAA868, the half-life of MAA868 ranged from 20-28 days following s.c. administration. Furthermore, a sustained PD effect of >2-fold mean activated partial thromboplastin time [aPTT] prolongation was observed for ~30 days and returned to the baseline level by ~60 days post-dose after a single 150 mg s.c. dose administration in study X2101. These data support monthly administration of MAA868. Furthermore, assessment of the exposure-response relationship of MAA868 in healthy subjects demonstrated a nearly flat exposure-response for relevant PD parameters (aPTT, FXI coagulation activity and free FXI) at concentrations above 4 µg/mL which is consistent with the Day 29 total MAA868 concentrations achieved with the 150 mg single dose administration in healthy subjects (CMAA868X2101).

Given the half-life of MAA868 and the observed time to return to baseline aPTT levels, a prolonged washout/follow-up period of approximately 110 days from the last dose of MAA868 should be a sufficient monitoring period for patients.

3.3. Selection of Doses in the Study

In the FIH study, single s.c. doses of MAA868 up to 240 mg was safe and well-tolerated. Up to the 150 mg dose, MAA868 produced robust and sustained dose-dependent inhibition of FXI and relevant prolongation of aPTT for approximately 4 weeks. MAA868 doses greater than 150 mg s.c. produced a sustained ~2-fold prolongation of aPTT for greater than 4 weeks.

The precise level of FXI inhibition to achieve a clinically meaningful anticoagulant effect remains unknown. The primary efficacy endpoint of this study will be the number of patients who achieve ≥ 50%, ≥ 80%, or ≥ 90% FXI inhibition [<50%, <20%, or 10% free FXI] at trough on Day 91 following s.c. administration of MAA868. Based on preliminary PK/PD modeling, the doses selected for cohorts 1 and 2 are projected to target the following levels of FXI inhibition:

- Cohort 1 (120 mg dose group). Targeted to achieve ≥ 50% FXI inhibition in 90% of subjects at trough (Day 91).
- Cohort 2 (180 mg dose group). Targeted to achieve ≥ 90% FXI inhibition in 90% of subjects at trough (Day 91).

Based on interim data, an optional cohort 3 may be dosed to add further data to the PK/PD model which will inform dose selection of MAA868 for subsequent studies.

The dosing regimens selected for evaluation in this study are projected to result in exposure (C_{max}) below the C_{max} achieved with a single dose of 240 mg s.c. in healthy subjects in the FIH study.

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

1. Written informed consent must be obtained before any assessment is performed
2. Male and female patients ≥ 18 and < 85 years old with paroxysmal atrial fibrillation (PAF) or atrial flutter on 12 lead electrocardiography at Screening
3. Patients with a history of PAF or atrial flutter, as documented by (telemetry, 12 lead electrocardiography or ambulatory [e.g. Holter] monitor) and not due to a reversible condition (e.g. alcohol binge drinking) can be entered even if they do not have PAF at Screening. There is not time-limit for this.
4. Patients with a CHA2DS2-VASc risk score (tool as a predictor for estimating the risk of stroke in patients with AF; Lip et al 2010) of 0-1 for men and 1-2 for women and in whom, in the investigator's judgment, the use of an anticoagulant for stroke prevention is not indicated
5. Body weight between 50 and 130 kg inclusive

4.2. Exclusion Criteria

1. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or until the expected PD effect has returned to baseline, whichever is longer; or longer if required by local regulations.
2. History of stroke, transient ischemic attack or systemic embolism
3. History of major bleeding during treatment with an anticoagulant or antiplatelet therapy. (Patients who have had major bleeding on anticoagulants or antiplatelet therapy more than a year ago can be enrolled only if the bleeding was due to a reversible cause, e.g. gastro-duodenal ulcer that was successfully treated.)
4. History of traumatic or non-traumatic intracranial, intraspinal or intraocular bleeding
5. Known bleeding diathesis or any known active bleeding site at screening or baseline
6. Family history of bleeding disorder
7. Known active GI lesions predisposing to bleeding events
8. Myocardial infarction, unstable angina pectoris or coronary artery bypass graft (CABG) surgery within 12 months prior to the Screening period
9. Known clinically significant valvular heart disease including moderate or severe mitral stenosis (valve area <1.5 cm^2).
10. Patients with a prosthetic heart valve
11. Uncontrolled hypertension defined as SBP/DBP ≥ 160/100 mmHg at the Screening visit
12. Patients with NYHA Class III- IV heart failure
13. Currently being treated with anticoagulant therapy or have been on anticoagulants in the previous 12 months. Potential patients who have been on anticoagulation more than 12 months ago requires discussion with the sponsor before enrolling.
14. Treatment with antiplatelet therapy such as either a P2Y12 inhibitor or aspirin. (Low dose aspirin ≤ 100 mg/d) is allowed.)
15. Severe renal impairment as defined as an estimated glomerular filtration rate ≤45 mL/min/1.73m^2 by the MDRD equation at the Screening Visit

16. Positive test for human immunodeficiency virus (HIV), positive hepatitis B (hepatitis B surface antigen [HBsAg]) or hepatitis C (anti-hepatitis C antibody [Anti-HCV]) at Screening
17. Significant illness, per Investigator judgement, which has not resolved within four (4) weeks prior to dosing
18. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during their time in the study. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment
    - Male sterilization of sexual partner (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
    - Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception

      In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.
      Women are considered post-menopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment with FSH is she considered not of child-bearing potential.
19. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
20. Patients with either a psychiatric disease or substance abuse history, which in the opinion of the Investigator could interfere with protocol compliance.
21. Any surgical or medical condition, which in the opinion of the Investigator, may place the patient at higher risk from his/her participation in the study, or is likely to prevent the patient from complying with the requirements of the study or completing the study.

4.3. Discontinuation Criteria

4.3.1. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Patients who do not meet the criteria for participation in this study may be rescreened.

4.3.2. Withdrawal of informed consent

Subjects may voluntarily withdraw from the study for any reason at any time.

Withdrawal from the study can occur when a subject chooses to do one or more of the following:

- Does not want to participate in the study anymore
- Does not want any further visits or assessments
- Does not want any further study-related contacts
- Does not allow analysis of already obtained biologic material.

If a subject who has received one or more doses or the study drug determines that they no longer want to participate the Investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason(s) for the subject's decision to withdraw his/her consent, record this information and conduct any assessments and visits still allowed.

In the event the subject withdraws consent prior to beginning dosing, the study treatment will not be administered. The data that would have been collected at subsequent visits will be considered missing. Further attempts to contact the subject are allowed when safety findings require follow-up.

4.3.3. Lost to Follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the Investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject cannot be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

4.4. Stopping Rules

Overall study stopping rules:

Enrollment in the study will be placed on hold if the Sponsor considers that the number and/or severity of AEs, abnormal safety monitoring tests or abnormal laboratory findings justify putting the study on hold.

The study may resume following the safety review, if the Investigator and Sponsor's Medical Monitor agree it is safe to proceed.

5. STUDY TREATMENTS

5.1. Treatments Administered

MAA868 drug product is a sterile, preservative-free liquid in vial for subcutaneous (s.c.) or intravenous (i.v.) administration. Each drug product vial contains 150 mg of MAA868 active ingredient per 1 mL plus 20% (0.2 mL) overfill which allows for complete withdrawal of the labeled dose (150 mg). [redacted] The excipients utilized are standard pharmacopoeial excipients that are commonly used in parenteral products. MAA868 will be provided as a 150 mg/mL solution in 6 mL single-use vials (with 1.2 mL fill). The 180 mg dose will require 2 vials. 0.8 and 1.2 mL should be withdrawn into a syringe and administered subcutaneously for the 120 mg and 180 mg doses, respectively.

Table 1: Overview of Study Medication

Study Treatment Name:	MAA868	Placebo
Dosage Formulation:	Liquid (in vial)	Liquid (in vial)
Unit Dose Strength(s)/Dosage Level(s):	150 mg/mL	Placebo to MAA868
Route of Administration:	SC injection	SC injection
Packaging and Labeling:	Study Treatment will be provided in vials. Each vial will be labeled as required per country requirement.	Placebo will be provided in vials. Each vial will be labeled as required per country requirement.
Provided by:	Anthos	Anthos

5.2. Preparation, Storage, Handling, and Accountability

Details on the requirements for storage and management of study treatment, and instructions to be followed for subject numbering, prescribing/dispensing and administering study treatment are outlined in the Pharmacy Manual.

MAA868 drug product vials should be stored refrigerated at 2°- 8°C and protected from light. A disposable syringe will be used to administer the s.c. injection.

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment. Only patients enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study treatment are provided in the Pharmacy Manual.

5.3. Method of Treatment Assignment

Subjects in each cohort will be randomized to MAA868 or placebo in a ratio of 12: 4 as follows.

- Cohort 1 = 120 mg MAA868 monthly s.c. or placebo
- Cohort 2 = 180 mg MAA868 monthly s.c. or placebo
- Cohort 3 (if necessary) = TBD mg MAA868 monthly s.c. or placebo

Randomization numbers will be assigned in ascending, sequential order to eligible subjects. The Investigator will enter the randomization number on the CRF.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A randomization list will be produced by or under the responsibility of Covance Drug Supply Management using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio. The randomization scheme for subjects will be reviewed and approved by a member of the Covance IIS Randomization Group.

Patients will be replaced at the Sponsor's discretion. Replacement subjects will be assigned randomization numbers 6101-6316 If a subject requires a replacement, the replacement subject will be assigned a randomization number corresponding to the original subject (e.g., Subject 6103 would replace Subject 1103).

The table below provides the general details of the numbering of the subjects for randomization:

Table 2: Randomization Assignment Numbering

Cohort	Randomization numbers	Replacement randomization numbers
I	1101-1116	6101-6116
II	1201-1216	6201-6216
III	1301-1316	6301-6316

5.4. Blinding

This is a subject- and investigator-blinded study. Subjects will remain blinded to study treatment throughout the study, except where indicated below.

The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

Site staff

With the exception of any unblinded pharmacist or pharmacy designee, all site staff (including study investigator and study nurse(s)) will be blinded to study treatment during treatment allocation and subject dosing. Appropriate measures must be taken by any unblinded pharmacist or pharmacy designee to ensure that the treatment assignments are concealed from the rest of the site staff.

Unblinding a single subject at the site for safety reasons (necessary for subject management) will occur via an emergency system in place at the site (see Section 5.10).

Site staff may also be unblinded to the treatment assignment of one or more subjects (within a single cohort or across cohorts as necessary), or an entire cohort at the initial cohort safety

evaluation timepoint if deemed appropriate to aid decision-making. The decision to un-blind site staff will be determined by the clinical trial team based on need or review of the entire study group will be performed at a pre-selected time.

Sponsor staff

The following unblinded Sponsor roles (or designee) are required for this study:

- Field monitor(s)
- Physician not directly involved study conduct
- Sample analyst(s) (PK blood)
- Study statistician
- Programmers and other personnel involved in study data analysis

An unblinded Covance Physician not directly involved in study conduct may receive a copy of the randomization schedule (via request to the Randomization Office), to facilitate analysis of aPTT safety labs that would otherwise unblind study Investigators. The unblinded Medical Monitor will alert the Investigator and Sponsor of any safety concerns.

The sample analysts will receive a copy of the randomization schedule (via request to the Randomization Office), to facilitate analysis of the samples. The sample analysts will provide the sample data to the study team under blinded conditions unless otherwise allowed.

The study statistician will be able to access the full randomization list from the start of the study and is allowed to share unblinded information with the rest of the clinical trial team as appropriate for internal decision purposes. For example, unblinded summaries and unblinded individual data can be shared with the team whenever necessary.

Study programmers and other personnel involved in study data analysis (e.g. biomarker expert, pharmacometrician, modeler(s)) are allowed to access treatment assignment information from the start of the study for the purpose of data analysis.

The clinical trial team is allowed to share unblinded results with other Sponsor staff (e.g. decision boards) as required for internal decision making on the study or the project while the study is ongoing.

All unblinded personnel will otherwise keep randomization lists and data or information that could un-blind other study team members confidential and secure except as described above.

Following final database lock all roles may be considered unblinded.

5.5. Treating the subject

MAA868 will be administered to the subject by study staff via s.c. administration. See the Pharmacy Manual for further details.

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

5.6. Permitted dose adjustments and interruptions of study treatment

Study treatment dose adjustments are not permitted. Any study drug administration that occurs outside of study visit windows must be approved by the study medical monitor.

5.7. Study Completion and Post-study Treatment

Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them.

Study completion is defined as when the last subject completes their EoS visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

All subjects will be required to attend the EoS visit and have related assessments collected as per the Schedule of assessments (Table 9). All SAEs reported during this time period must be reported as described in Section 7.6.2 and the Safety Management Plan. Documentation of attempts to contact the subject should be recorded in the source documentation.

5.8. Discontinuation of Study Treatment

The Investigator may decide to suspend the s.c. administration of the study drug if symptoms or signs consistent with an injection site reaction or hypersensitivity reaction occur.

Subjects who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 4.3.2, Withdraw of Informed Consent). Where possible, they should return for the EoS assessments indicated in the assessment table. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in Section 4.3.3 (Lost to follow-up). This contact should preferably be done according to the study visit schedule.

5.9. Study Termination

The study can be terminated by Anthos at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. Should this be necessary, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject and followed until the aPTT has returned to baseline. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The Investigator will be responsible for informing the Institutional Review Board (IRB) of the early termination of the trial.

5.10. Emergency breaking of assigned treatment code

Emergency unblinding must only be undertaken when it is essential to treat the subject safely and efficaciously, such as in the event of clinically significant bleeding events. Most often, knowledge of the possible treatment assignments is sufficient to treat a study subject who presents with an emergency condition. A complete set of emergency code break cards will be provided to the Investigator site(s) and a complete set will be available at Anthos and Covance. All code break cards must be retained until the end of the study and retained by the site as a source document.

They must be stored in a secure place but be accessible to the Investigator 24 hours per day in case of emergency. The Investigator will receive a blinded code break card for each subject. In an emergency, the code break may be opened to determine the treatment. There is no known reversal agent for MAA868 (see Section 6.2).

The code break should not be opened for any reason other than an emergency. If the Investigator opened the code break, he/she must note the date, time, and reason for removing it and retain this information with the case report form documentation. The unblinded treatment code must not be recorded on the CRF. The Investigator must also immediately inform the study monitor that the code has been broken.

It is the Investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the code break cards at any time in case of emergency. The Investigator will need to provide:

- Protocol number
- Study drug name (if available)
- Subject number.

In addition, the Investigator must provide oral and written information to inform the subject how to contact his/her backup in cases of emergency when he/she is unavailable to ensure that un blinding can be performed at any time.

6. CONCOMITANT THERAPIES

6.1. Concomitant therapy

The Investigator must instruct the subject to notify the study staff of any new medications (including nutritional supplements and herbal medications) that he/she takes after being enrolled into the study.

All prescription medications, OTC drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the Investigator should contact Covance before randomizing a subject or, if the subject is already enrolled, to determine if the subject should continue participation in the study.

During the study, in the event the Investigator elects to start the patient on chronic antithrombotic therapy, anticoagulation or antiplatelet therapy should not be started until the patient's aPTT has returned to baseline.

Reporting medication errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient/subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

All study treatment errors and uses outside of what is foreseen in the protocol will be collected in the Dose Administration Record CRF. Study treatment errors are only to be reported to Covance DSS department if the treatment error is associated with an SAE.

All instances of misuse or abuse must be documented in the AE CRF irrespective of the misuse/abuse being associated with an AE/SAE. In addition, all instances of misuse or abuse must be reported to the Covance DSS department. As such, instances of misuse or abuse are also to be reported using the SAE form/CRF.

Table 3 summarizes the reporting requirements.

Table 3: Summary of reporting requirements for medication errors

Treatment error type	Document in Dose Administration CRF	Document in AE CRF	Complete SAE form/CRF
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see Section 7.6.1 and Section 7.6.2, respectively.

6.2. Study restrictions

Women of child-bearing potential

Women of child-bearing potential are not permitted to participate in this study, unless they agree to use highly effective methods of contraception during their time in the study.

Prohibited treatment

Use of the following medications is not allowed during the course of the study from screening (Visit 1) through the EoS. Patients who are receiving such medication(s) will be excluded, or if ethically and clinically justified, the medication(s) should be gradually withdrawn at least seven days before the baseline visit:

- Use of chronic antiplatelet agents such as clopidogrel or ticagrelor is prohibited; however, use of low-dose aspirin (≤100 mg per day) is permitted.
- Use of chronic systemic anticoagulants such as warfarin, low molecular weight heparin or heparinoids, or direct oral anticoagulants such as apixaban or dabigatran. Patients may be started on chronic anticoagulation during the Washout/Follow-up period once their aPTT has returned to baseline, at the Investigator's discretion.
- Use of any therapeutic monoclonal antibody regardless of the indication during the study.

Dietary restrictions

- No alcohol for 48 hours before each clinic visit (from Screening through the EoS visit). During the study, alcohol consumption will be restricted to no more than 2 drinks/day for males and 1 drink/day for females.
- Patients should not make significant alterations in their diet (e.g., going on weight loss diet) while in the study.
- During the study, caffeinated beverages will be restricted to no more than 3 cups/day.

Other restrictions

No strenuous physical exercise or activities which have an increased risk of injury or falling should be undertaken until after the EoS visit.

6.3. Reversal medication

There is currently no specific antidote for MAA868. FXI concentrates (not marketed in the US) are unlikely to be effective as the excess in free MAA868 concentrations in the circulation is expected to quickly neutralize the exogenous FXI.

Recombinant FVIIa can bypass the hypocoagulopathy and restore hemostasis in patients with severe FXI deficiency. Administration of intermediate to high doses of rFVIIa (40 to 90 µg/kg) resulted in supra-physiological levels of FVII and thromboembolic complications in patients with severe FXI deficiency (Riddell et al 2011). Low doses of rFVIIa are associated with lower prothrombotic risk. Riddell et al reported their experience in 4 patients with severe FXI deficiency undergoing surgery (Riddell et al 2011); patients were administered rFVIIa 30 µg/kg and tranexamic acid 1 g i.v. at induction of anesthesia. Subsequent bolus doses of rFVIIa 15–30 µg/kg were administered at 2 to 4 hourly intervals as guided by rotational thromboelastometry for 24 48 hours and tranexamic acid 1 g every 6 hourly for 5 days. Low doses of rFVIIa and tranexamic acid were safe and effective in restoring hemostasis in severe FXI deficiency in this study. In another study comprising 4 patients with severe FXI deficiency with inhibitor who experienced 5 surgeries (Livnat et al 2009), 1 g of tranexamic acid was given 2 hours before surgery, immediately prior to the interventions then every 6 hour for at least 7 days; moreover, rFVIIa was administered at doses ranging from 15 to 30 µg/kg at the completion of surgery. This protocol secured normal hemostasis in patients with severe FXI deficiency with inhibitor.

Based on the above, rFVIIa can be recommended as a preferred therapeutic option to restore hemostasis in subjects with active, non-accessible bleeding site and in subjects requiring immediate reversal of the MAA868 PD effects prior to an urgent surgery. Please see the Investigator's Brochure - Summary of the data and guidance for the investigator for a more complete discussion.

7. STUDY ASSESSMENTS AND PROCEDURES

7.1. Assessment schedule

Subjects should be seen for all visits/assessments as outlined in the assessment schedule (Table 9).

Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the study treatment discontinuation (TD) visit will be performed. At the TD visit, all dispensed investigational product should be reconciled, and the AE and concomitant medications recorded on the CRF.

7.2. Informed consent procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB-approved informed consent.

The Sponsor, or Sponsor designee, will provide to investigators a proposed informed consent form that complies with the ICHE6 Good Clinical Practice (GCP) guideline and regulatory requirements and is considered appropriate for this study. The informed consent form will also include a section related to optional future research which will require a separate signature if the subject agrees to future research. Any changes to the proposed consent form suggested by the Investigator must be agreed to by the Sponsor before submission to the IRB.

Information about common side effects already known about the investigational drug can be found in the IB. This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and then must be discussed with the subject.

Ensure subjects are informed of the contraception requirements outlined in the Section 4.2 (Exclusion criteria).

A copy of the approved version of all consent forms must be provided to the Covance monitor after IRB approval.

7.3. Subject screening

In general, it is permissible to re-screen a subject if s/he fails the initial Screening or falls out of the screening window timelines; however, each case must be discussed and agreed with the Sponsor Medical Monitor on a case-by-case basis. A new screening number will be assigned to a subject who is re screened, thus no screening number will be used twice.

Reasons for screen failure will be documented in the site log.

7.4. Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data will be collected on all subjects. Relevant medical history/current medical conditions data will also be collected until signature of informed consent.

Investigators have the discretion to record abnormal test findings on the medical history CRF, if in their judgment, the test abnormality occurred prior to the informed consent signature.

Hepatitis screen, HIV screen

All subjects will be screened for HIV, Hepatitis B and C.

Alcohol test and drug screening

All subjects will be screened for alcohol and substances of abuse.

7.5. Efficacy Assessments

The PD samples will be collected at the timepoints defined in the Assessment schedule (Table 9). Follow instructions outlined in the Central Laboratory Manual regarding sample collection, numbering, processing and shipment.

In order to better define the PD profile, the timing of the sample collection may be altered based on emergent data. The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol.

PD samples will be obtained and evaluated in all subjects at all dose levels.

7.5.1. Free FXI

Free FXI concentrations (FXI that is not bound to MAA868) will be measured in plasma. A detailed description of the assay methods will be included in the Bioanalytical Data Report.

7.5.2. aPTT

aPTT, calibrated for FXI deficiency, and aPTT using a standard laboratory protocol will be measured at all timepoints indicated in the Assessment schedule (Table 9).

aPTT will be determined in plasma. The detailed method descriptions of the assay will be included in the Bioanalytical Data Report.

7.5.3. Total FXI

Total FXI concentrations (FXI that is either bound to MAA868 or free) will be measured in plasma. A detailed description of the assay methods will be included in the Bioanalytical Data Report.

7.5.4. FXI coagulation activity (FXI:C)

FXI:C will be measured in plasma. A detailed description of the assay methods will be included in the Bioanalytical Data Report.

7.6. Safety Assessments

Safety assessments are specified below; assessments will be collected as specified in the Assessment Schedule (Table 9).

Bleeding

All suspected bleeding events will be documented by the Investigator in the appropriate CRF. All suspected bleeding events will be adjudicated by experienced medical personnel that is blinded to

treatment assignment. Adjudication of bleeding events will be performed in accordance with the International Society of Thrombosis and Haemostasis (ISTH) definition of a major bleeding in non-surgical patients (Schulman et al 2005) and criteria for clinically-relevant non-major bleeding (CRNM) events. The definitions of bleedings are as follows:

Major bleeding events include:

- Fatal bleeding, and/or
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or
- Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more or leading to transfusion of two or more units of whole blood or red cells.

CRNMs (clinically relevant non-major) bleeding events will be defined as clinically overt bleeding that did not satisfy the criteria for major bleeding and that led to:

- hospital admission, or
- physician-guided medical treatment, or
- surgical treatment or
- change in antithrombotic therapy

In addition to the ISTH definition of bleeding events other definitions such as TIMI, BARC,

GUSTO, etc. can be used as supportive for exploratory safety analyses.

The population is those who have received at least one dose of the study drug.

Major cardiovascular, cerebrovascular, and venous thromboembolic events

All suspected major cardiovascular, cerebrovascular, and VTE events will be documented by the Investigator in the appropriate CRF including any diagnostic imaging that was used to confirm the event. For instance, any suspected episodes of DVT (i.e., swelling, localized pain, redness, heat, localized warmth) must be documented by compression ultrasound (CUS) or venography.

Any suspected episodes of PE (i.e., shortness of breath, chest pain, coughing, tachycardia, hemoptysis, hemodynamic compromise, unexplained death) must be documented by ventilation/perfusion lung scintigraphy, spiral computed tomography (sCT), or pulmonary angiography.

All major cardiovascular, cerebrovascular, systemic arterial, and venous thromboembolic events (VTEs) including deaths for which a major cardiovascular, cerebrovascular, or VTE event could not be ruled out will be adjudicated by experienced medical personnel that is blinded to treatment assignment.

The adjudicated outcome will be the basis for any interim and final safety evaluations.

7.6.1. Adverse Events

An AE is any untoward medical occurrence [i.e., any unfavorable and unintended sign (including abnormal laboratory findings), symptom or disease] in a subject or clinical investigation subject after providing written informed consent for participation in the study until the EoS visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the study treatment are also considered an AE irrespective if a clinical event has occurred. See Section 7.6.2 for an overview of the reporting requirements.

The occurrence of AEs must be sought by non-directive questioning of the subject at each visit during the study. AEs also may be detected when they are volunteered by the subject during or between visits or through physical examination finding, laboratory test finding, or other assessments.

Abnormal laboratory values or test results constitute AEs only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in healthy subjects. Investigators have the responsibility for managing the safety of individual subject and identifying AEs. Alert ranges for liver and kidney related events are included in Appendix 1 and Appendix 2, respectively. Additional clinically notable laboratory values are included in Appendix 3.

AEs must be recorded on the AE CRF under the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

1. Severity grade

- mild: usually transient in nature and generally not interfering with normal activities
- moderate: sufficiently discomforting to interfere with normal activities
- severe: prevents normal activities

2. Relationship to the study treatment

- Related
- Possibly related
- Not related

3. Duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.

4. Whether it constitutes a SAE (see Section 7.6.2 for definition of SAE) and which seriousness criteria have been met

5. Action taken regarding investigational treatment.

All AEs must be treated appropriately. Treatment may include one or more of the following:

- no action taken (e.g. further observation only)
- concomitant medication or non-drug therapy given
- hospitalization/prolonged hospitalization (see Section 7.6.2 for definition of SAE)

6. Outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown).

Information about common side effects already known about the investigational drug can be found in the IB. Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the investigational drug, the interventions required to treat it, and the outcome.

The Investigator must also instruct each subject to report any new AE (beyond the protocol observation period) that the subject, or the subject's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the Investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Covance.

7.6.2. Reporting Serious Adverse Events

Definition of SAE

An SAE is defined as any AE [appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s)] which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - elective or pre-planned treatment for a pre-existing condition and has not worsened since the start of study drug
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - social reasons and respite care in the absence of any deterioration in the subject's general condition
    - is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (see Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (see Annex IV, ICH-E2D Guideline).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All AEs (serious and non-serious) are captured on the CRF; SAEs also require individual reporting to Covance Drug Safety & Epidemiology (DS&E) as per Section 0.

SAE Reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last planned study assessment, must be reported to Covance within 24 hours of learning of its occurrence as described below. Any SAEs experienced after this period should only be reported to Covance if the Investigator suspects a causal relationship to study treatment.

Note: SAEs reported by subjects deemed to be screen failures must be reported to Covance as outlined here with appropriate information also captured in the CRFs.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the Investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Follow- up information provided must describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable) and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the IB (new occurrence) and is thought to be related to the study treatment a Covance DS&E associate may urgently require further information from the Investigator for Health Authority reporting. Covance may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Follow the detailed instructions outlined in the Safety Management Plan regarding the submission process for reporting SAEs to Covance. Note: SAEs must be reported to Covance within 24 hours of the Investigator learning of its occurrence/receiving follow-up information.

7.7. Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events must be followed.

Please refer to Appendix 1 for complete definitions of liver events.

Follow-up of liver events

Every liver event defined in Appendix 1 should be followed up by the Investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 4 of Appendix 1.

- Repeating liver chemistry tests (ALT, AST, total bilirubin (TBL), PT/INR, ALP and γGT) to confirm elevation within 48-72 hours.

  These liver chemistry repeats should always be performed using the central laboratory, with the results provided via the standard electronic transfer. If results will not be available from the central laboratory within 24 hours, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results reported on the unscheduled local laboratory CRF.

- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to Section 4.3 (Discontinuation of study treatment), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
    - Repeating liver chemistry tests two or three times weekly. Testing should include ALT, AST, ALP, PT/INR, and γGT. If total bilirubin is elevated > 2 x ULN, fractionation into direct and indirect bilirubin is required. To rule out muscular origin of transaminase elevations, CPK should be measured along with liver chemistry tests. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic. Retesting should be continued up to resolution.
    - Obtaining a more detailed history of symptoms and prior or concurrent diseases.
    - Obtaining a history of concomitant drug use (including non-prescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.

- Exclusion of underlying liver disease, as specified in Table 6.
- Imaging such as abdominal US, CT or MRI, as appropriate
- Obtaining a history of exposure to environmental chemical agents.
- Considering gastroenterology or hepatology consultations.

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF.

7.8. Renal safety monitoring

Every renal laboratory trigger or renal event must be followed up by the Investigator or designated personnel at the trial site. Recommended follow-up assessments are listed in Appendix 2.

7.9. Pregnancy

All female study participants, regardless of the requirement to be of non-child-bearing potential to be enrolled into this study, will have pregnancy testing. See the Assessment Schedule (Table 9), for timing of the protocol required pregnancy testing; additional pregnancy testing may be performed to meet local requirements*. Subjects will not receive study medication in case of a positive urine or serum pregnancy test.

*If additional pregnancy testing is needed per local requirements, those additional results will be kept as source documentation only.

Pregnancy reporting

Reproductive toxicity and teratogenicity data are not available for this antibody at this time, therefore no guidelines on therapeutic recommendations in case of pregnancy are available. This study enrolls women who are considered to be of non-child-bearing potential, thus pregnancy is not an expected outcome for any female study participant. However, in the case that a pregnancy in a female study participant should occur please follow the below reporting guidelines. The follow-up for this subject and for the fetus is at the discretion of the Investigator.

To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Covance within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the Investigator to the local Covance DSS department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

All assessments that are considered as a risk during pregnancy must not be performed. The subject may continue all other protocol assessments.

7.10. Clinical Laboratory Evaluations

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Covance personnel. The results should be evaluated for criteria defining an AE and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Covance personnel should be contacted.

Safety labs (hematology, clinical chemistry and urinalysis) do not need to be repeated at baseline if the Baseline visit is taking place within 48 hours of the screening labs being collected from an individual subject.

Subjects should be instructed to fast for at least 8 hours prior to scheduled safety lab collections.

Clinically notable laboratory findings are defined in Appendix 3.

Hematology

Hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differentials and platelet count will be measured.

Clinical chemistry

Sodium, potassium, creatinine, BUN/urea, uric acid, chloride, albumin, calcium, alkaline phosphatase, total bilirubin, bicarbonate/HCO_3, LDH, GGT, AST, ALT, CK, glucose, total cholesterol, triglycerides. If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

Urinalysis

Dipstick measurements for specific gravity, protein, glucose and blood will be performed. Microscopy, WBC, RBC and sediments will also be assessed in case of an abnormal dipstick test.

Special clinical laboratory evaluations

Stool samples will be collected to check for occult blood at screening and baseline. Screening fecal samples can be collected at any time during the Screening period, and baseline fecal samples must be collected within 72 hours of Day 1. If fecal screening samples are collected within 72 hours of Day 1, then they do not need to be repeated for the Baseline visit. In the event that a subject is unable to produce a stool sample for sampling, the site medical staff may elect to produce a sample via digital extraction from the rectum.

Details regarding collection methods and processing are outlined in the Central Laboratory Manual.

7.11. Vital Signs, Physical Examination, and Other Safety Evaluations

Vital signs will include the collection of oral body temperature (recorded in °C), blood pressure (BP)–sitting and standing –and pulse measurements. At Screening, for eligibility determination, three sets of systolic and diastolic BP and pulse rate measurements will be collected after the subject has been sitting for 3 minutes, with back supported and both feet placed on the floor and

the mean will be used to determine eligibility. A single set of BP and pulse rate measurements will then be collected after three minutes in the standing position.

A single set of sitting BP measurements will be collected at subsequent visits.

Physical exams will include assessment of general appearance, skin, lymph nodes, HEENT, neck, thorax/lungs, cardiovascular, abdomen, musculoskeletal, and neurological systems.

Height in centimeters (cm) and body weight [to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes] will be measured. Body mass index (BMI) will be calculated using the following formula:

BMI = Body weight (kg) / [Height (m)]$_2$. BMI results will be documented in the CRF to 2 decimal places.

7.12. Electrocardiogram (ECG)

The ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. PR interval, QRS duration, heart rate, RR interval, QT, QT corrected by the Fridericia correction formula (QTcF) will be collected. The QTcF should be used for clinical decision-making. ECGs must be collected, analyzed and appropriately signed and archived at the study site; the site will also store all ECG readings digitally (if possible). For any ECGs with subject safety concerns, duplicate ECGs must be performed to confirm the safety finding. Clinically significant ECG findings at baseline must be discussed with the Sponsor before administration of study treatment. Clinically significant abnormalities must be reported in the AE CRF.

7.13. Pharmacokinetic Analysis

The PK samples will be collected at the timepoints defined in the Assessment schedule (Table 9). Follow instructions outlined in the Central Laboratory Manual regarding sample collection, numbering, processing and shipment. See Section 7.13 regarding the potential use of residual samples.

In order to better define the PK profile, the timing of the PK sample collection may be altered based on emergent data. The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol. Changes to the PK Assessment schedule, if any, will be communicated to the sites in the dose adjustment minutes.

The PK samples will be obtained and evaluated in all subjects at all dose levels. Untreated (placebo) samples will not be analyzed.

Concentrations of plasma total MAA868 (i.e. MAA868 that is bound to FXI or not bound to FXI) will be determined by a validated LC-MS/MS method. A detailed description of the method used to quantify the concentration of total MAA868 will be included in the bioanalytical raw data and in the Bioanalytical Data Report.

All concentrations below the LLOQ or missing data will be labeled as such in the concentration data listings.

For standard PK abbreviations and definitions see the list provided at the beginning of this protocol.

The following PK parameters will be determined, where data permit, using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.2 or higher): C_0 (the concentration at the end of infusion), AUC_{last}, AUC_{inf}, C0/D, and AUC/D, based on the plasma concentration data.

The linear trapezoidal rule will be used for AUC calculation. The terminal half-life of MAA868 ($T_{1/2}$), volume of distribution (V_{ss}) and clearance (C_L) will also be estimated, if feasible, based on the data.

7.14. Other assessments

7.14.1. Exploratory Biomarker assessments

Biomarkers including, but not limited to, D-Dimer and biomarkers of thrombogenesis and coagulation may also be studied.

The list may be changed or expanded further, as it is recognized that more relevant or novel biomarkers may be discovered during the conduct of the study.

Sample(s) will be collected at the timepoint(s) defined in the Assessment schedule (Table 9).

Follow instructions for sample collection, numbering, processing and shipment provided in the central lab manual. Detailed descriptions of the assays will be included in the Bioanalytical Data Reports.

7.14.2. Immunogenicity (IG)

The IG samples will be collected at the timepoints defined in the Assessment schedule (Table 9).

Follow instructions outlined in the Central Laboratory Manual regarding sample collection, numbering, processing, and shipment. See Section 7.13 regarding the potential use of residual samples.

Immunogenicity analytical method(s)

A ligand-binding assay will be used to detect anti-MAA868 antibodies. The analytical method will be described in detail in the IG Bioanalytical Data Report.

7.15. Use of residual biological samples

Residual blood samples may be used for another protocol specified endpoint.

Any residual samples remaining after the protocol-defined analysis has been performed may be used for additional exploratory analysis. This may include but is not limited to using residual samples for protein binding, metabolite profiling, biomarkers of transporters or metabolic enzyme activity (such as 4-beta-hydroxycholesterol levels) or other bioanalytical purposes (e.g. cross check between different sites and/or stability assessment). Given the exploratory nature of the work, the analytical method used for those assessments may not be validated. As such, the results from this exploratory analysis will not be included in the clinical study report.

8. SAMPLE SIZE AND DATA ANALYSES

8.1. Determination of Sample Size

A sample size of 16 subjects per treatment dose cohort with a ratio of 3:1 for MAA868 and placebo treatment assignment is based on historic data considerations. For example, if the observed proportion of patients in a cohort achieving target levels of inhibition is 11/12, the 90% confidence interval would be 0.66 to 0.996.

8.2. Analysis Populations

All Randomized Set will include all subjects who are randomized

Full Analysis Set will include randomized subjects excluding those subjects who are randomized into the study in error and did not receive study drug. Subjects will be analyzed based on the assigned treatment at the randomization.

Per Protocol Set will include subjects in Full Analysis Set and those subjects have no major protocol deviation after randomization.

Safety Set will include randomized subjects who at least received one dose of study drug. Subjects will be analyzed based on the actual treatment taken.

PK/PD Analysis Set will comprise all subjects who received at least one dose of study drug and have at least one PK/PD assessment. Subjects will be analyzed based on the actual treatment taken.

8.3. General Considerations

All efficacy analysis will be based on the Full Analysis Set or Per Protocol Set and will be performed based on the assigned treatment arm at the randomization. Only descriptive statistics will be summarized, no statistical inference will be calculated in efficacy.

Safety analysis will be performed using Safety Set. Subjects will be analyzed based on the actual treatment taken.

PK and PD analysis will be based on PK/PD Analysis Set.

Continuous variables will be summarized by number of subjects [n], mean, standard deviation [SD], median, minimum [min], and maximum [max]. Categorical variable will be summarized using frequency [N] and percentage [%].

8.4. Demographics and Baseline characteristics

All baseline summaries will be based on the All Randomized Set and Full Analysis Set populations.

Gender, race and ethnicity will be summarized using counts and percentages. Age, height (cm), and weight (kg) will be summarized with descriptive statistics (number of subjects [n], mean, SD, median, minimum [min], and maximum [max]). Age may be summarized by decades using N and %.

The listing of subjects with abnormal physical examination findings at screening will be presented. The number and percent of subjects with medical history events will be summarized. Vital signs

collected at screening (sitting diastolic and systolic blood pressure, pulse, temperature and body weight) will be summarized with descriptive statistics (n, mean, SD, median, min, and max).

8.5. Efficacy Analysis

8.5.1. Primary Efficacy Outcome Measures

Within each treatment cohort patients will be randomized 3:1 to active drug or placebo.

The primary analysis variable is whether a subject will achieve a certain percentage FXI inhibition at trough (Day 91). The response rate per treatment group will be calculated by number of subjects who achieve targeted FXI inhibition rate divided by the total number of subjects in the treatment group. The dose regimens and targeted FXI inhibition achievement for Cohorts 1 and 2 are as follows

Cohort 1 (MAA868 120 mg monthly or placebo): Targeted to achieve ≥ 50% FXI inhibition in 90% of subjects at trough (Day 91).

Cohort 2 (MAA868 180 mg monthly or placebo): Targeted to achieve ≥ 90% FXI inhibition in 90% of subjects at trough (Day 91).

The "on treatment" trough FXI levels will be used for the primary analysis, where "on treatment" FXI level is defined as a value which is collected within 30 (±5) days after the last administration of MAA868. The estimate of the responder rate (%) at Day 91 will be presented for each dose regimens of MAA868 together with 2-sided 90% confidence intervals (CI) computed via the Clopper-Pearson exact binomial method.

8.5.2. Secondary Efficacy Outcome Measures

The secondary efficacy analysis is to evaluate the proportion of subjects achieving FXI inhibition ≥ 50%, ≥80%, and ≥90% at trough after the first and second dose (Day 31 and Day 61) at 3 dose levels of MAA868. The analyses described for the primary endpoint will be repeated for the secondary efficacy variables as follows:

- Cohort 1 (MAA868 120 mg monthly or placebo): at Day 31 and 61.
- Cohort 2 (MAA868 180 mg monthly or placebo): at Day 31 and 61
- Cohort 3 (MAA868 TBD mg monthly or placebo): at Day 31 and 61

8.6. Safety Analysis

The safety evaluation includes the analysis of bleeding events, AEs, major cardiovascular, cerebrovascular, systemic arterial, and venous thromboembolism events, laboratory data, ECG, vital signs, hypersensitivity reactions, injection site reactions, and development of anti-drug antibodies. All safety analysis will be performed using the Safety Set.

8.6.1. Adverse Events

The Investigator's verbatim term of each AE will be mapped to system organ class (SOC) and preferred term (PT) using the MedDRA dictionary.

Treatment-emergent Adverse Events (TEAEs) will be of primary interest. The TEAEs will be summarized by SOC and PT; a subject will only be counted once per SOC and once per PT within a treatment. If a subject reports more than one AE with the same PT, the AE with the maximum severity will be presented. Subject counts and percentages and event counts will be presented for each treatment and totaled for all treatments for the following summaries:

- All TEAEs
- Serious TEAEs
- All TEAEs by severity
- All TEAEs by relationship to study drug
- TEAEs potentially related to study drug
- TEAEs potentially related to study drug by severity
- TEAEs leading to discontinuation of study drug
- TEAEs leading to withdrawal from the study

Adverse events of special interest (AESI) will be reported for a selection of interested AE terms that are specific to Sponsor's product and program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor can be appropriate.

The AESIs for this study are defined as follows:

1. TERM 1
2. TERM 2

Similarly, to the TEAE summary, the AESI will be summarized in the following:

1. All AESIs
2. Serious AESIs
3. All AESIs by severity
4. All AESIs by relationship to study drug
5. AESIs leading to discontinuation of study drug
6. AESIs leading to withdrawal from the study

No statistical inference between the treatments will be performed on AEs.

Listings will be presented by subject for all TEAEs, AESIs, as well as for SAEs, TEAEs associated with outcome of death, and TEAEs leading to discontinuation from the study.

8.6.2. Bleeding Events

An analysis will be performed for the composite safety endpoint of major and CRNM bleeding events which occur on-treatment from the first dose of the study drug to the last dose of the study drug + 30 days if the subject permanently discontinues the study drug prior to the third dose on Day 91. The number of events and the incidence of adjudicated bleeding events will be tabulated

based on ISTH definition by treatment including the composite endpoint of major bleeding events and/or CRNM bleedings.

Major bleeding events (Yes/No)

CRNM bleeding events (Yes/No)

Total bleeding events (Yes/No)

If a subject has more than one bleeding event in each above category, the subject will be counted only once in the tabulation.

The adjudicated outcome will be the basis for any interim and final analysis.

8.6.3. Major cardiovascular, cerebrovascular, and venous thromboembolic events

An analysis will be performed for the composite safety endpoint of major cardiovascular, cerebrovascular, and venous thromboembolic events which occur on-treatment from the first dose of the study drug to the last dose of the study drug + 30 days if the subject permanently discontinues the study drug prior to the third dose on Day 91.

The number of events and the incidence of adjudicated events will be tabulated based on the outcomes adjudicated by experienced medical personnel, and the adjudicated outcome will be the basis for any interim and final analysis.

8.6.4. Clinical Laboratory Evaluations

Clinical laboratory results in continuous values at each timepoint and for change from baseline will be displayed using summary statistics (n, mean, median, SD, minimum and maximum values).

A laboratory value that is within the central laboratory's reference range will be considered normal. A laboratory value that is outside the central laboratory's normal range will be considered abnormal and will be flagged as either high (H) or low (L). The number and percentage of subjects with abnormal laboratory values will be summarized for each scheduled visit. In addition, shift tables will be presented to display the shift in the normal range categories (L, normal [N], H) from baseline to specified timepoint. Laboratory results in clinical significance will also be summarized in tabulation.

All clinical laboratory data will be presented in listings. Baseline is defined as the result obtained prior to first administration of study medication. Laboratory data will be summarized in SI units.

8.6.5. Vital Sign Measurements

Pre-dose values, post-dose values, and the change from baseline in vital sign measurements (sitting diastolic and systolic blood pressure, pulse, temperature and body weight) will be summarized with descriptive statistics (n, mean, SD, median, min, and max) at each timepoint by treatment. The baseline value will be value just prior to first administration of study medication.

8.6.6. ECG Parameters

The ECG measures (QTc-B, QTc-F, QT, RR, ventricular rate, PR, and QRS) will be listed and summarized with descriptive statistics (n, mean, SD, median, min, and max) at each timepoint by treatment.

The listings of subjects with abnormal ECG results, as judged by the Investigator, will be displayed and will be calculated. The baseline will be the value just prior to first administration of study medication.

8.7. Pharmacokinetic Analysis

Descriptive summary statistics will be provided by treatment and visit/sampling timepoint with descriptive statistics (n, mean, SD, median, min, and max) at each timepoint by treatment. An exception to this is T_{max} where median, minimum and maximum will be presented.

Concentrations below the lower limit of quantitation (LLOQ) will be treated as zero in summary statistics and for PK parameter calculations. A geometric mean will not be reported if the dataset includes zero values.

Individual total MAA868 plasma concentration data will be listed by treatment (MAA868 arms only), subject, and visit/sampling timepoint. PK parameters will also be listed by treatment and subject.

8.8. Biomarkers

Coagulation parameters, including free and total FXI, FXI:C, and immunogenicity will be summarized by timepoint and treatment.

8.9. Interim Analysis

Safety and tolerability data (AEs, laboratory assessments, vital signs and ECG data) will be evaluated from Cohort 1 by the Sponsor's Medical Monitor and Covance Lead Project Physician after approximately 10 of the patients in cohort 1 have received their second dose of study drug and have been followed for at least an additional 14 days. The decision to proceed to cohort 2 will be made only after it is confirmed that the cohort 1 dose was safe and tolerated and all planned subjects in cohort 1 have been randomized. If notable AEs or safety concerns are found in cohort 1, the study may be terminated.

Likewise, after approximately 10 of the patients in cohort 2 have received their second dose of study drug and have been followed for at least an additional 14 days, safety, tolerability, and other analyses will be evaluated.

Additional IAs may be conducted to support decision making concerning the current clinical study, the Sponsor’s clinical development projects in general or in case of any emergent safety concerns. The Investigator(s) may be included for decisions with regards to any unplanned IAs that address questions of subject safety.

Unblinded IA results will be reviewed by the Sponsor (or their designees).

No further dissemination of interim results should occur, in particular not with individuals involved in treating the study’s subjects or assessing clinical data (e.g. ECGs, symptoms) obtained in the study.

8.10. Data Quality Assurance

Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Covance representative will review the protocol and CRFs with the Investigator(s) and their staff. During the study Covance employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The monitor will visit the site to check the completeness of subject records, the accuracy of entries on the CRFs, the adherence to the protocol and to GCP, the progress of enrollment, and ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits.

The Investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The Investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Covance monitoring standards require full verification for the presence of informed consent, adherence to the eligibility criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

Data collection

Designated Investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the electronic data capture (EDC) system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to Covance working on behalf of Anthos. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the Investigator will receive copies of the subject data for archiving at the investigational site.

Data not requiring a separate written record are noted on the Assessment schedule (Table 9) and can be recorded directly on the CRF. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

Database management and quality control

Covance will review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. Site personnel will complete and sign the faxed copy and fax it back to Covance who will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally, and the results will be sent electronically to Covance.

At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Covance.

The occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked, and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Anthos Head of Regulatory and the Chief Medical Officer.

9. ETHICAL CONSIDERATIONS

9.1. Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

9.2. Responsibilities of the Investigator and IRB

Before initiating a trial, the Investigator/institution must obtain approval/favorable opinion from the IRB for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Covance monitors, auditors, Covance Quality Assurance representatives, designated agents of Anthos, IRBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the Investigator must inform Anthos immediately that this request has been made.

For multi-center trials, a Coordinating Investigator will be selected by Anthos around the time of Last Patient Last Visit to be a reviewer and signatory for the CSR.

9.3. Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. Upon study completion and finalization of the study report the results of this trial will be posted in a publicly accessible database of clinical trial results in accordance with local regulations.

No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement between the Sponsor and the investigator and/or the investigator's institution.

The information developed from this clinical study will be used by the Sponsor in connection with the development of MAA868 and other drugs and diagnostics, and thus may be disclosed as required to other clinical investigators, business partners, or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the Sponsor with all data obtained in the study.

10. PROTOCOL ADHERENCE

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances is an Investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an Investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Anthos and approved by the IRB and health authorities, where required, it cannot be implemented.

10.1. Protocol Amendments

Any change to the protocol can only be made in a written protocol amendment that must be approved by Anthos, Health Authorities where required, and the IRB prior to implementation.

Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB is notified.

Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7.6.2 (Safety Monitoring) must be followed and the Study Lead informed.

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12. APPENDICES

12.1. Appendix 1 - Liver Event Definitions and Follow-up Requirements

Table 4: Liver Event Definition

Definition	Thresholds
Potential Hy's law cases	• ALT or AST > 3 X ULN and TBL > 2 × ULN without initial increase in ALP to > 2 × ULN
ALT or AST elevation with coagulopathy	• ALT or AST > 3 × ULN and INR > 1.5 (in the absence of anticoagulation)
ALT or AST elevation accompanied by symptoms	• ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash, or eosinophilia
Isolated ALT or AST elevation	• ALT or AST > 8 × ULN • 5 x ULN < ALT/AST ≤ 8 x ULN • 3 x ULN ALT/AST 5 x ULN
Isolated ALP elevation	• ALP > 2 × ULN (in the absence of known bone pathology)
Others	• Any clinical event of jaundice (or equivalent term) Any adverse event potentially indicative of liver toxicity

Table 5: Action required for Liver Events

Criteria	Action required
Potential Hy's law cases ALT or AST elevation with coagulopathy ALT or AST elevation accompanied by symptoms Isolated ALT or AST elevation > 8 X ULN Jaundice	• Hospitalize, if clinically appropriate • Establish causality • Complete CRFs per liver event guidance
Isolated ALT or AST elevation > 5 to ≤ 8 X ULN	• Establish causality • Complete CRFs per liver event guidance
Isolated ALT or AST elevation > 3 to ≤ 5 × ULN (patient is asymptomatic)	• Monitor liver chemistry tests two or three times weekly
Isolated ALP elevation	• Repeat liver chemistry tests within 48-72 hours • If elevation is confirmed, measure fractionated ALP; if >50% is of liver origin, establish hepatic causality • Complete CRFs per liver event guidance
Any AE potentially indicative of liver toxicity	• Hospitalize if clinically appropriate • Complete CRFs per liver event guidance

Table 6: Exclusion of underlying Liver Disease

Disease	Assessment
Hepatitis A, B, C, E	• IgM anti-HAV; HBSAg, IgM anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	• ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	• Ethanol history, γGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	• Ultrasound or MRI
Hypoxic/ischemic hepatopathy	• Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI
Biliary tract disease	• Ultrasound or MRI, ERCP as appropriate
Wilson disease	• Caeruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-anitrypsin

12.2. Appendix 2 - Specific Renal Alert Criteria and Actions

Table 7: Specific Renal Alert Criteria and Actions

Criteria	Action required
Serum creatinine (sCr) increase 25 – 49% compared to baseline	• Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase ≥ 50%	• Consider causes and possible interventions • Repeat assessment within 24-48 hours if possible • Consider hospitalization and specialized treatment
Protein-creatinine or albumin-creatinine ratio increase ≥ 2-fold, or new onset dipstick proteinuria ≥ 1+ , or Albumin-creatinine ratio (ACR) ≥ 30 mg/g or ≥ 3 mg/mmol, or Protein-creatinine ratio (PCR) ≥ 150 mg/g or >15 mg/mmol	• Consider causes and possible interventions • Assess serum albumin and serum protein • Repeat assessment to confirm
New onset glucosuria on urine dipstick (unless related to concomitant treatment, diabetes)	<u>Assess and document:</u> • Blood glucose (fasting) • Serum creatinine • Urine albumin-creatinine ratio
New hematuria on dipstick	<u>Assess and document</u> • Urine sediment microscopy • Assess sCr and urine albumin-creatinine ratio • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

Additional specialized assessments are available to assess renal function or renal pathology.
(Note: In exceptional cases when a nephrologist considers a renal biopsy, it is strongly recommended to make specimen slides available for evaluation by Anthos to potentially identify project-wide patterns of nephrotoxicity.)
Whenever a renal event is identified, a detailed subject history and examination are indicated to identify, document and potentially eliminate risk factors that may have initiated or contributed to the event:

- Blood pressure assessment (after 5 min rest, with an appropriate cuff size)
- Signs and symptoms such as fever, headache, shortness of breath, back or abdominal pain, dysuria, hematuria, dependent or periorbital edema
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output
- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other potential causes of renal dysfunction, e.g., dehydration, hemorrhage, tumor lysis

Table 8: Follow-up renal events

Action	Follow up
Assess*, document and record in the CRF or via electronic data load. Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc.) in the CRF	• Urine dipstick and sediment microscopy • Blood pressure and body weight • Serum creatinine, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate, and uric acid • Urine output
Monitor subject regularly (frequency at Investigator's discretion) until:	• Event resolution: (sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline) OR • Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.

*Urine osmolality: in the absence of diuretics or chronic kidney disease this can be a very sensitive metric for integrated kidney function that requires excellent tubular function. A high urinary osmolality in the setting of an increase in sCr will point toward a "pre-renal" cause rather than tubular toxicity.

12.3. Appendix 3 - Clinical notable laboratory values

Clinical notable laboratory values:

The definition, the specific alert criteria and the corresponding actions for hepatic and renal notable laboratory abnormalities are respectively provided in Appendix 1 and Appendix 2.

The following laboratory values are considered clinically notable and should be forwarded to Covance at the same time that they are sent to Investigators:

- A change from baseline in hemoglobin ≥ 2 g/dL
- A decrease from baseline in platelets count ≥ 50% or < 100 x 10^9/L
- A positive fecal occult blood test
- Macroscopic hematuria

Whenever a clinically notable laboratory value is identified, a detailed subject history and examination are indicated to identify, document and potentially eliminate a bleeding event:

- Blood pressure assessment (after 5 min rest, with an appropriate cuff size);
- Signs and symptoms such as shortness of breath, tiredness, abdominal pain, hematemesis, rectorrhagia, melena, gingival or nose bleeding, bruising and hematoma;
- Concomitant events or procedures such as trauma, surgical procedures.

When one of the above occurs the action plan is as follows:

- Confirm the value, assess and document the clinically notable laboratory value in the CRF or via electronic data load;
- Investigate the underlying causes such as clinical or subclinical bleeding event and the contributing factors such as intake of prohibited medications;
- Monitor subject regularly (frequency at Investigator's discretion) until resolution or stabilization. Hospital admission, additional laboratory tests, endoscopy, volume replacement, transfusion, etc. should be performed at the Investigator's discretion and according to the medical needs (see Section 6.3 for reversal therapy).

12.4. Appendix 4 - Schedule of Assessments

Table 9: Schedule of Assessments

Period	Screening	Treatment						Washout / Follow-up				
Visit	1	2	3	4	5	6	7	8	9	10	TD	EoS
Day	-28 to -3	1 (pre-dose)	11	31	41	61	71	91	101	121	-	170
Window			±2	±2	±3	±2	±3	±2	±3	±3		±10
Informed consent	X											
Medical history	X											
Smoking & alcohol history	X											
I/E criteria	X	X										
Physical Exam	X	X	X	X		X		X		X	X	X
Height	X											
Weight	X	X										X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X						X				X
HIV, Hepatitis B, Hepatitis C	X											
aPTT, Free and total FXI	X	X	X	X	X	X	X	X	X	X	X	X
aPTT (corrected for FXI), FXI:C		X				X		X				X
PK assessment: total MAA868		X	X	X	X	X	X	X	X	X		X
Antidrug antibodies (ADA)		X		X		X	X	X		X		X
Exploratory biomarker collection	X	X		X		X		X		X		
Complete safety Labs	X	X	X	X	X	X		X		X	X	X
Pregnancy test	Serum	Urine			Urine			Urine			Urine	Urine
Urine dipstick	X	X	X	X	X	X		X		X	X	X
Fecal occult blood test	X	X										
AE collection	X											
Concomitant meds	X											
Local assessment of CV and cerebrovascular events		X										
Local assessment of bleeding events		X										
Dispense Study Medications		X		X		X						
Drug Accountability		X		X		X		X				
MAA868		X		X		X						
Placebo		X		X		X						

Period	Screening	Treatment						Washout / Follow-up				
Visit	1	2	3	4	5	6	7	8	9	10	TD	EoS
Day	-28 to -3	1 (pre-dose)	11	31	41	61	71	91	101	121	-	170
Window			±2	±2	±3	±2	±3	±2	±3	±3		±10
Injection site inspection		X	X	X	X	X	X					
Study disposition								X			X	X
TD = Study treatment discontinuation; EoS = End of Study; FXI:C = Factor XI coagulation activity												