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ANTHOS THERAPEUTICS, INC.

Abelacimab (MAA868)

Clinical Trial Protocol ANT-006

A Multicenter, RandomiZed, Active-ControLled Study to Evaluate the Safety and Tolerability of Two Blinded Doses of Abelacimab (MAA868) Compared with Open-Label Rivaroxaban in Patients with Atrial Fibrillation (AZALEA)

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[redacted]	[redacted]

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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Principal Investigator's Statement and Signature:

I, the undersigned, have read protocol ANT-006 (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:

_____

_____

_____

_____

[redacted]

Notification of serious adverse events

Dear Investigator,

You must report a serious adverse event (SAE) (initial or follow-up) to [redacted] as summarized below. Refer to Section 8.4 of the protocol for SAE criteria and additional requirements. Further details on the method of reporting a SAE will be provided to sites.

- Complete SAE report
- Submit SAE report to [redacted]) within 24 hours after awareness of the SAE

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List of abbreviations

ADA	anti-drug antibodies
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AF	Atrial Fibrillation
ALT	alanine aminotransferase
ALP	alkaline phosphatase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under concentration time curve
BMI	body mass index
BUN	blood urea nitrogen
CDC	complement dependent cytotoxicity
CEC	Clinical Endpoint Committee
CFR	Code of Federal Regulation
CRNM	clinically relevant non-major
CRO	Contract Research Organization
CSR	clinical study report
CV	coefficient of variation
DMC	Data Monitoring Committee
DOAC	direct oral anticoagulant(s)
DVT	deep vein thrombosis
EC	Ethics Committee
eCRF	electronic case report/record form
ECG	electrocardiogram
EDC	electronic data capture
EoE	End of Extension Treatment
EoS	End of Study
EoT	End of Treatment
FcγRs	Fc gamma receptors
FIH	first-in-human
FFP	fresh frozen plasma
FXI	factor XI
FXIa	activated factor XI
FXI-ASO	FXI-antisense oligonucleotide
FXI:C	FXI coagulation activity

FXI_f	free factor XI
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
γ-GT	gamma-glutamyl transferase
HIV	human immunodeficiency virus
HR	hazard ratio
IB	investigator's brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICF	informed consent form
IG	immunogenicity
IN	investigator notification
IRB	Institutional Review Board
ISR	injection site reaction
ISTH	International Society on Thrombosis and Haemostasis
i.v.	intravenous
IxRS	Interactive Web or Voice Response System
K_d	equilibrium dissociation constant
kg	kilogram(s)
LLOQ	lower limit of quantification
LMWH	low molecular weight heparin
mAbs	monoclonal antibodies
MCV	mean corpuscular volume
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram(s)
MI	myocardial infarctions
mL	milliliter(s)
NOAEL	no observed adverse effect level
OTC	over the counter
PCC	prothrombin complex concentrate
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
p.o.	by mouth; orally
PT	prothrombin time

PRO	patient-reported outcome(s)
PSDD	permanent study drug discontinuation
[redacted]	[redacted]
QoL	Quality of Life
RBC	red blood cell(s)
RDW	red cell distribution width
rFVIIa	recombinant activated factor VII
SAE	serious adverse event
s.c.	subcutaneous
sCr	serum creatinine
SoC	standard of care
SSC	Study Steering Committee
SUSAR	suspected unexpected serious adverse reactions
TAFI	thrombin activable fibrinolysis inhibitor
TBL	total bilirubin
TIA	transient ischemic attack
TIMI	The Thrombosis In Myocardial Infarction (TIMI) Study Group
TGA	thrombin generation assay
TKA	total knee arthroplasty
TXA	tranexamic acid
ULN	upper limit of normal
VKA	vitamin K antagonists
VTE	venous thromboembolism
WBC	white blood cell(s)
WOCBP	women of child-bearing potential

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
Dosage	Dose of the study treatment given to the patient in a time unit
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (i.e., prior to starting any of the procedures described in the protocol)
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 patient who is screened but is not treated or randomized
Patient or subject	A trial participant
Patient or Subject number	A unique number assigned to each patient upon signing the informed consent. This number is the definitive, unique identifier for the patient and should be used to identify the patient throughout the study for all data collected, sample labels, etc.
Randomization number	A unique identifier assigned to each randomized patient, 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 patient permanently stops taking the assigned 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 patient 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 which has not already been analyzed, and does not allow further use of already obtained biologic material for future research.

[redacted]

Protocol synopsis

Protocol Number	ANT-006
Full Title	A Multicenter, Randomized, Active-Controlled Study to Evaluate the Safety and Tolerability of Two Blinded Doses of Abelacimab (MAA868) Compared with Open-Label Rivaroxaban in Patients with Atrial Fibrillation
Brief Title	Randomized, Active-Controlled Study to Evaluate Two Blinded Doses of Abelacimab (MAA868) Compared with Rivaroxaban in Patients with Atrial Fibrillation
Sponsor and Clinical Trial Phase	Anthos Therapeutics, Inc. Phase 2b
Intervention Type	Biologic
Study Type	Interventional
Purpose and Rationale	The purpose of the ANT-006 study is to evaluate the bleeding profile of abelacimab relative to rivaroxaban in patients with Atrial Fibrillation (AF) at moderate-to-high risk of stroke
Primary Objective	• To evaluate the effect of abelacimab relative to rivaroxaban on the rate of major or clinically relevant non-major (CRNM) bleeding events
Secondary Objective(s)	• To evaluate the effect of abelacimab relative to rivaroxaban on the rate of major bleeding events • To evaluate the effect of abelacimab relative to rivaroxaban on the rate of major or minor bleeding events
Study Design	This is an event-driven, randomized, active-controlled, blinded endpoint, parallel-group study to evaluate the effects of two blinded doses of abelacimab relative to open-label rivaroxaban on the rate of major or CRNM bleeding events in patients with AF who are at moderate-to-high risk of stroke. Patients with AF who are at moderate-to-high risk of ischemic stroke will be enrolled. Randomization into treatment groups will be stratified by the use of concomitant antiplatelet use at baseline (yes/no) and renal function (CrCl ≤50 ml/min or CrCl >50 ml/min). The study is comprised of up to 4 periods: 1) screening (up to 4 weeks), 2) study drug treatment period through the end of treatment period (EoT) visit, 3) an optional extension period beginning at the EoT visit for qualifying patients on their randomized study treatment at the EoT visit who also meet the inclusion/exclusion criteria for the extension period and provide written informed consent to receive open-label abelacimab treatment, and 4) a transition period to appropriate standard of care (SoC) antithrombotic therapy per the discretion of the investigator through the End of Study (EoS) visit.
Population	Approximately 1,200 male and female patients with AF at moderate-to-high risk of stroke in whom anticoagulation therapy is indicated and planned for the duration of the study.

Key Inclusion criteria	1. Able to provide written informed consent before any study assessment is performed 2. Male and female patients ≥ 55 years old 3. History of AF or atrial flutter with planned indefinite anticoagulation. Patients with newly diagnosed AF are eligible. 4. A CHA_2DS_2-VASc of ≥4 OR a CHA_2DS_2-VASc of ≥3 with at least 1 of the following: • Planned concomitant use of antiplatelet medication (i.e., aspirin and/or P2Y12 inhibitor) for the duration of the trial • CrCl ≤50 ml/min by the Cockcroft-Gault equation
Key Exclusion criteria	1. Use of other investigational drugs within 5 half-lives prior to enrollment or until the expected pharmacodynamic effect has returned to baseline, whichever is longer 2. History of hypersensitivity to any of the study drugs (including rivaroxaban) or its excipients, to drugs of similar chemical classes, or any contraindication listed in the label for rivaroxaban 3. Patients with an intracranial or intraocular bleed within the 3 months prior to screening 4. Clinically significant mitral stenosis (valve area <1.5 cm2) 5. Mechanical heart valve or other indication for anticoagulation therapy other than atrial fibrillation (e.g., venous thromboembolism) 6. Known presence of an atrial myxoma or left ventricular thrombus 7. History of left atrial appendage closure or removal 8. Active endocarditis 9. Systolic BP >180 mm Hg or diastolic BP >100 mm Hg on repeated measurements at screening 10. Planned invasive procedure with potential for uncontrolled bleeding (e.g., major surgery) 11. Any stroke within 14 days before randomization or TIA within 3 days before randomization 12. A CrCl <15 mL/min or on dialysis at the time of Screening 13. Platelet count ≤70,000/mm^3 at the Screening Visit 14. Hemoglobin <8 g/dL at the Screening Visit 15. aPTT or PT >1.5x the upper limit of normal (ULN) at the Screening Visit, if the patient is not on an anticoagulant
Study treatment	Allocation 1:1:1 • Abelacimab (MAA868) 90 mg subcutaneously (s.c.) monthly • Abelacimab (MAA868) 150 mg s.c. monthly • Rivaroxaban 20 mg by mouth (p.o.) once per day with evening meal [Note: Patients with a CrCl ≤50 ml/min by the Cockcroft-Gault equation will receive the 15 mg p.o. daily dose of rivaroxaban]

Statistical considerations	Assuming a hazard ratio (HR) of 0.60 for each dose of abelacimab compared with rivaroxaban, at least 166 primary outcome events will provide at least 80% power for each abelacimab arm vs. rivaroxaban with a 2-sided alpha of 0.05. Approximately 1,200 patients should provide the requisite number of events over an estimated trial duration of 27 months. The primary analysis will compare each abelacimab regimen with rivaroxaban for the time to first occurrence of major or CRNM bleeding in the On-Treatment Analysis Set. For each treatment regimen, the event rate will be estimated with 95% confidence intervals (CIs). The time to first event will be analyzed using the Cox proportional hazards model including treatment and the following two stratification factors as covariates: 1. Planned use of concomitant antiplatelet medication use (i.e., aspirin and/or P2Y12 inhibitor) for the duration of the trial 2. CrCl (Cockcroft-Gault) $\leq$ 50 ml/min
Key words	Randomized, prospective, blinded endpoint evaluation, abelacimab, MAA868, rivaroxaban, atrial fibrillation

1 Introduction

1.1 Background

Atrial fibrillation (AF) is the most common abnormal heart rhythm encountered in clinical practice, accounting for approximately one third of hospitalizations for cardiac dysrhythmias. This common cardiac arrhythmia is estimated to affect approximately 2.3 million in the United States (US) and more than 6 million individuals in Europe. These figures are projected to grow rapidly because of the aging population and the associated increase in age-related co-morbidities that predispose individuals to AF (Rahman et al 2014).

AF is associated with a 4- to 5-fold increase in embolic stroke, with the absolute risk dependent on age as well as other risk factors (January et al 2014). The risk of stroke associated with AF rises with age to 23.5% for patients aged 80 to 89 years; thus, most patients with AF require life-long therapy with anticoagulation to prevent stroke and other systemic embolic events. The CHA_2DS_2-VASc risk score is a validated and widely used stratification tool to predict thromboembolic risk in AF patients and to identify patients who should benefit from anticoagulation therapy (Lip et al 2010; January et al 2014; Hindricks et al 2020). It is estimated that 85 to 90% of AF patients require anticoagulation therapy.

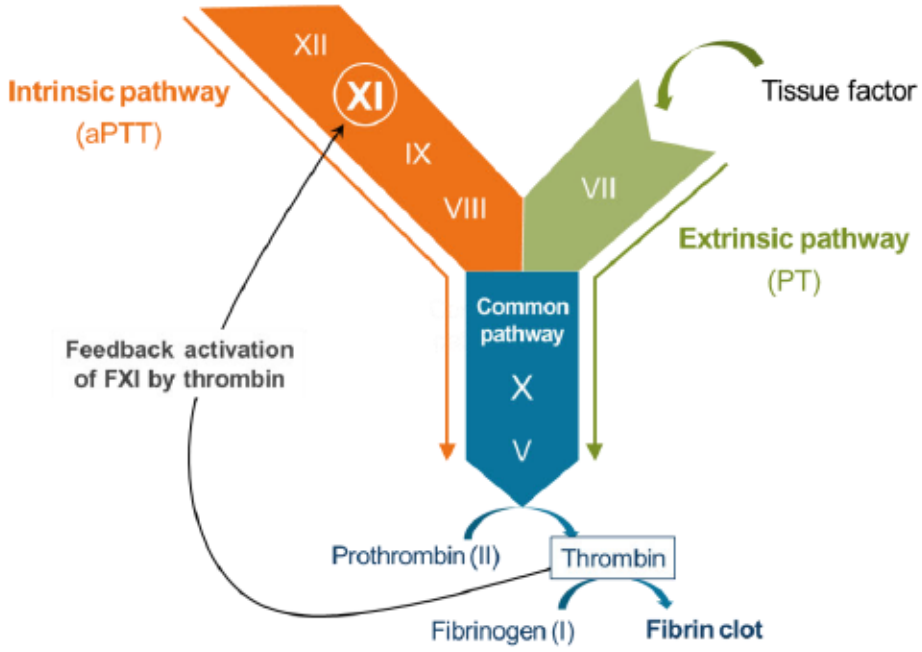
Anticoagulation with either direct oral anticoagulant drugs (DOACs) or vitamin K antagonists (VKA), such as warfarin, have been demonstrated to be effective in reducing the risk of stroke and systemic embolism (January et al 2014; Hindricks et al 2020). In a meta-analysis that included data from four pivotal phase 3 clinical trials of DOACs for stroke prevention in patients with AF, treatment with DOACs was associated with a reduced risk of stroke and systemic embolic events and were safer with respect to serious or life-threatening bleeding, particularly intracranial hemorrhage, although there was an increase in gastrointestinal bleeding observed with several DOACs (Ruff et al 2014). Though DOACs are safer than warfarin, there remains a significant risk of bleeding with existing agents which continues to limit the use of anticoagulants in patients with AF. Registry studies indicate substantial rates of undertreatment, particularly in high-risk patient populations who are at increased risk of both thromboembolic and major bleeding events (Huisman et al 2017). Thus, there remains an unmet medical need for a hemostasis-sparing anticoagulant therapy effective in reducing the risk of thromboembolic events, but with a lower risk of bleeding events.

Factor XI (FXI) serves as a crucial link between the intrinsic (contact-activation) pathway and the common pathway of the coagulation cascade (Figure 1-1). In the classic view of the coagulation cascade, activation of the intrinsic pathway leads Factor XII to activate FXI, which ultimately leads to activation of the common pathway and the generation of fibrin—an enzymatic cascade that is reflected in the activated partial thromboplastin time (aPTT), a commonly performed laboratory test. But it is now established that during in vivo hemostasis, the initial thrombin that is generated by tissue factor activation of the extrinsic pathway can also activate FXI, leading to amplification in the generation of thrombin (Figure 1-1) (Gailani and Renné 2007; Cheng et al 2010).

Several lines of evidence, however, suggest that FXI-mediated amplification of thrombin generation may be dispensable for physiologic hemostasis. In fact, thrombin-mediated activation of FXI may actually play a deleterious role by promoting the formation of pathologic thrombi that lead to ischemic strokes and systemic emboli. This is illustrated by rare individuals born with an inherited deficiency of FXI. Characterization of these individuals indicate that they are at lower risk of ischemic stroke and venous thromboembolism (VTE) compared to the general population (Salomon et al 2011; Preis et al 2017). At the same time, spontaneous

bleeding in these individuals is rare, and bleeding events that they do experience are typically mild and occur in tissues associated with high fibrinolytic activity such as the oral mucosa, nasal mucosa, and urinary tract (Duga and Salomon 2013). A similar phenotype has been recapitulated in non-human primate studies where FXI inhibition has been shown to lead to a reduction in thrombus formation without an increased risk of bleeding (Crosby et al 2013). Conversely, population studies suggest that increased circulating levels of FXI are associated with an increased risk of stroke and VTE events (Meijers et al 2000; Suri et al 2010).

Figure 1-1 Coagulation cascade with activation of Factor XI by thrombin



A clinical trial of antisense oligonucleotide mediated suppression of FXI (FXI-ASO) demonstrated antithrombotic efficacy in patients undergoing elective unilateral total knee arthroplasty (TKA) (Büller et al 2015). In this study, patients randomized to the FXI-ASO groups were started on treatment 36 days before surgery and achieved approximately 60% and 80% levels of FXI inhibition in the 200 mg and 300 mg dose groups, respectively, on the day of the surgery. Patients in the FXI-ASO 200 mg dose group had similar antithrombotic efficacy to standard of care prophylaxis with s.c. enoxaparin, while patients in the FXI-ASO 300 mg dose group had a statistically significant reduction in the rate of total VTE events compared to standard of care prophylaxis with s.c. enoxaparin (4% vs. 30%, $P<0.001$). Strikingly, inhibition of FXI in patients undergoing TKA did not result in an increased risk of bleeding compared to enoxaparin. Patients in both FXI-ASO dose groups had fewer postoperative major and clinically relevant non-major (CRNM) bleeding events suggesting that FXI inhibition in patients undergoing orthopedic surgery has antithrombotic efficacy with no increase in bleeding compared to enoxaparin. Similar results were observed in a clinical study of a monoclonal antibody inhibitor of activated FXI, osocimab, also in patients undergoing elective TKA (Weitz et al 2020).

Overall, these results suggest that inhibiting FXI may lead to effective anticoagulation with an improved safety profile over existing antithrombotic drugs in terms of bleeding.

1.2 Abelacimab (MAA868)

Abelacimab (MAA868) is a fully human monoclonal antibody that binds the catalytic domain of FXI in both the zymogen and activated factor XI (FXIa) forms with high affinity and potency (Koch et al 2019). In preclinical studies, administration of abelacimab dose-dependently prolonged the activated partial thromboplastin time (aPTT) in vitro. In vivo, a single subcutaneous (s.c.) dose of abelacimab at a 3 mg/kg dose in cynomolgus monkeys led to a sustained prolongation of aPTT that lasts more than a month. Furthermore, in an experimental model of carotid artery thrombosis induced by $FeCl_3$ in $FXI^{-/-}$ mice reconstituted with human FXI, dose-dependent prolongation of the aPTT was associated with the prevention of carotid artery thrombosis.

Further details can be found in the abelacimab Investigator's Brochure (IB).

1.2.1 Additional pre-clinical studies

[redacted]

1.2.2 Human Studies with abelacimab

Clinical experience with abelacimab, including results from completed studies and ongoing studies in patients, is summarized below.

Phase 1 studies

In the first-in-human (FIH) study (CMAA868X2101), single SC administration of abelacimab up to 240 mg was safe and well-tolerated in healthy subjects (Koch 2019). The incidence of adverse events (AEs) was comparable across abelacimab dose groups and the pooled placebo group. No bleeding events, hypersensitivity reactions (HSRs), or injection site reactions (ISRs) were reported. Increasing doses of abelacimab were associated with >90% reductions in free FXI concentrations. The reduction in free FXI levels was associated with a dose and time-dependent prolongation of the aPTT. The onset of robust reductions in free FXI and FXI coagulation activity (FXI:C), as well as aPTT prolongation, were observed approximately 12-

24 hours after SC administration of doses in the expected therapeutic range of abelacimab. Subcutaneous doses up to 150 mg resulted in a mean aPTT prolongation of >2-fold from baseline through Day 29, while doses >150 mg up to the top dose tested, 240 mg, extended the duration of aPTT prolongation up to and through Day 43, without any further aPTT prolongation. Analysis of pharmacokinetic (PK) data from a high body mass index (BMI ≥35 kg/m2) cohort administered 240 mg demonstrated that higher BMI was associated with a modest reduction in abelacimab exposure and a moderately shorter duration of aPTT prolongation. Low titer levels of anti-drug antibodies (ADA) were detected in some subjects exposed to abelacimab at 1 or more sampling time points. ADA formation was not associated with AEs or any detectable effects on PK or pharmacodynamics (PD).

In the CMAA868A1101 study, a single SC administration of abelacimab up to 150 mg was safe and well tolerated in healthy Japanese subjects. There were no serious adverse events (SAEs) or study discontinuations due to AEs. All AEs were mild in severity, and the incidence of AEs was similar between the abelacimab dose groups and placebo. No bleeding events, HSRs, or ISRs were reported. The PK/PD profile of abelacimab in healthy Japanese subjects was generally comparable to the PK/PD profile observed in the FIH study. Although ADAs were detected in subjects at various time points, there was no indication that PK/PD or safety was affected.

In the ANT-003 study, single intravenous (IV) administration of abelacimab up to 150 mg was safe and well-tolerated in healthy subjects (Yi 2022). At 1 hour after the start of the IV infusion (the first timepoint assessed), abelacimab produced >99% reduction in free FXI concentrations and increases in aPTT consistent with the expected PD effects of abelacimab. At higher doses, the PD effects of abelacimab were sustained for at least 4 weeks and returned to baseline by Day 106 (end of study). Consistent with the results from the FIH study, the PK exposure of abelacimab and duration of FXI inhibition was moderately lower in patients with a high BMI, possibly due to the observed larger volume of distribution and slightly faster clearance of abelacimab. Aside from changes in aPTT, no clinically relevant changes in the clinical laboratory tests and electrocardiogram (ECG) parameters were observed. No bleeding events occurred, and no HSRs or ISRs were reported.

Phase 2 studies

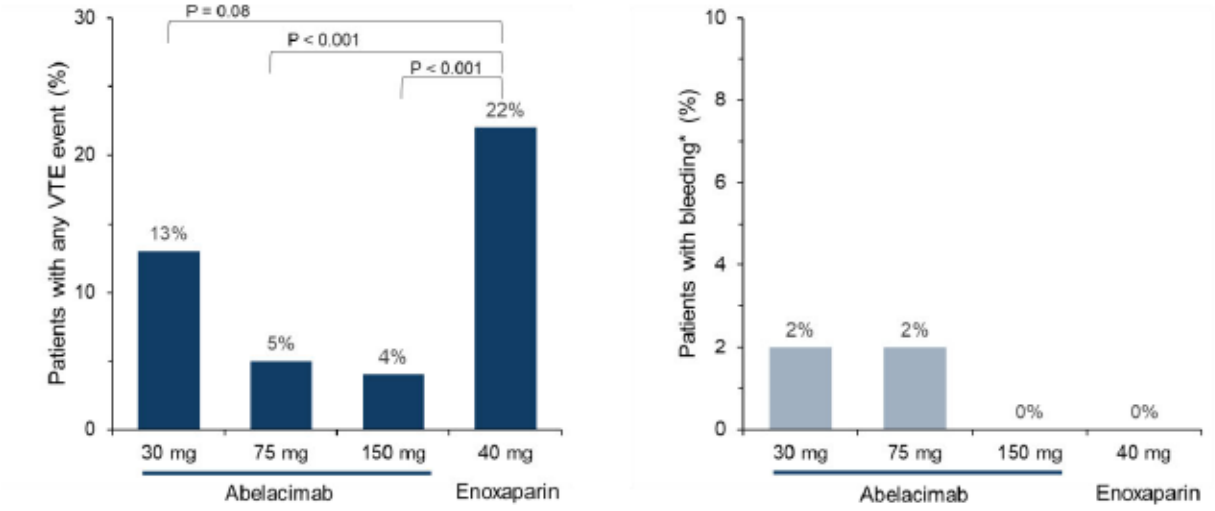
Venous thromboembolism prevention study

The ANT-005 study was a multicenter, randomized, active-controlled, dose-ranging study to compare the efficacy and safety of 3 blinded doses of IV abelacimab compared to open-label thromboprophylaxis with SC enoxaparin in patients undergoing elective unilateral TKA (Verhamme 2021). Patients were randomized to receive one of 3 doses of abelacimab IV once approximately 4-8 hours after surgery or standard of care (SoC) thromboprophylaxis with enoxaparin up to the protocol mandated ascending venography on Day 10, that was adjudicated by a blinded independent adjudication committee. Results demonstrated that IV administration of abelacimab after TKA surgery was associated with a dose-dependent reduction in the rate of VTE events (Figure 1-2). The rate of VTE in the enoxaparin group was 22%. By comparison, the rate of VTE in the abelacimab 30 mg group (13%) was non-inferior to enoxaparin, while the rate of VTE in the abelacimab 75 mg (5%; $p<0.001$) and 150 mg dose groups (4%; $p<0.001$) were superior to enoxaparin demonstrating that abelacimab has robust antithrombotic efficacy.

There were no deaths or HSRs, and the percent of patients who experienced an AE was similar in the abelacimab and enoxaparin groups. Bleeding occurred in 2%, 2%, and none of the patients in the 30, 75, and 150 mg abelacimab groups, respectively, and in none of the patients in the enoxaparin group (Figure 1-2). All major or CRNM bleeding events in abelacimab

patients were associated with the surgical site. A total of 6 SAEs were reported in 5 abelacimab patients. Three SAEs of 'periprosthetic joint infection' reported in abelacimab patients were judged as 'possibly related' to treatment by the Investigator.

Figure 1-2 Summary of the ANT-005 Study



*includes major or clinically relevant nonmajor bleeding events adjudicated by an independent adjudication committee that was blinded to treatment assignment

Atrial fibrillation studies

ANT-004 was a randomized, patient-and-Investigator-blinded, placebo-controlled study that evaluated the safety, tolerability, PK, and PD effects of monthly SC administration of abelacimab in AF patients with a CHA2DS2-VASc score of 0-1 in men or 1-2 in women (Yi 2022). A total of 18 patients were randomized, 8 in Cohort 1 (120 mg SC abelacimab or matching placebo) and 10 in Cohort 2 (180 mg SC abelacimab or matching placebo). Repeat SC administration of abelacimab up to 180 mg for 3 months was safe and well tolerated. There were no deaths or SAEs, and no major or CRNM events were reported. In addition, no HSRs or ISRs were reported.

ANT-006 is an ongoing, event-driven, randomized, active-controlled, parallel-group Phase 2b study to evaluate the safety and tolerability of 2 blinded doses of abelacimab compared to open-label rivaroxaban on the rate of major or CRNM bleeding events in patients with AF at moderate-to-high risk of stroke. Patients were randomly assigned 1:1:1 to abelacimab 90 mg SC monthly, abelacimab 150 mg SC monthly, or rivaroxaban oral (PO) daily. Randomization was stratified by concomitant antiplatelet use at baseline and renal function at screening. The 90 and 150 mg abelacimab doses were selected based on a PK/PD model that predicted that these doses would achieve levels of FXI inhibition that bracket the clinically efficacious range. At near steady-state, the 90 mg dose is predicted to provide approximately 80% FXI inhibition at trough while the 150 mg dose is predicted to provide approximately 97% FXI inhibition at trough. The primary safety endpoint is the composite of major and CRNM bleeding events centrally adjudicated by an independent Clinical Events Committee (CEC) blinded to treatment assignment. An independent program-wide Data Monitoring Committee (DMC) is providing oversight of the safety of study participants.

Enrollment was complete in December 2021. A total of 1,287 subjects were randomized with 335 subjects in North America (US and Canada), 896 subjects in EU countries (Czech Republic, Hungary, and Poland), and 56 subjects in Asia (Korea and Taiwan). The mean age of subjects is 73.9 years (range 55-93 years), 44% are female, the mean CHA2DS2-VASc score is 4.7, approximately 20% have a creatinine clearance $\leq$50 mL/min (Cockcroft-Gault equation),

and approximately 24% were on concomitant antiplatelet therapy at baseline. As of September 2022, the mean time of a patient on treatment in the ANT-006 study is greater than 12 months and there are patients who have been followed for 1.5 years.

Phase 3 studies of abelacimab in patients with cancer-associated thrombosis (ongoing)

Under IND [redacted] abelacimab is being developed to reduce the risk of recurrent VTE in patients with cancer-associated thrombosis (CAT). The ANT-007 and ANT-008 Phase 3 studies are summarized below.

ANT-007

The ANT-007 study is a global Phase 3 prospective, randomized, open-label, blinded endpoint evaluation (PROBE), active controlled study to evaluate whether abelacimab administered once monthly is non-inferior to twice daily (BID) oral apixaban in terms of VTE recurrence in patients with cancer and recently diagnosed VTE. ANT-007 is planned to enroll approximately 1655 subjects with cancer and symptomatic/ incidental proximal lower leg deep vein thrombosis (DVT) and/or either symptomatic pulmonary embolism (PE) or incidental PE. The study primary endpoint is to demonstrate noninferiority of abelacimab for preventing VTE recurrence relative to apixaban. [redacted]. An independent CEC blinded to treatment assignment will review and adjudicate key endpoint events including cause of death, suspected DVT, suspected PE, and bleeding events.

ANT-008

The ANT-008 study is a global Phase 3 PROBE, active controlled study to assess whether abelacimab administered once monthly is non-inferior to once daily (QD) SC injection of dalteparin in preventing VTE recurrence in patients with gastrointestinal/genitourinary (GI/GU) cancers and recently diagnosed VTE. ANT-008 is planned to enroll approximately 1020 subjects with GI/GU cancer and a newly diagnosed, objectively confirmed symptomatic or incidentally detected proximal lower-limb DVT, symptomatic PE, or incidentally detected PE. The study primary endpoint is to demonstrate noninferiority of abelacimab for preventing VTE recurrence relative to dalteparin. [redacted] An independent CEC blinded to treatment assignment will review and adjudicate key endpoint events including cause of death, suspected DVT, suspected PE, and bleeding events.

The Phase 3 ANT-007 and ANT-008 studies were initiated in the first half of 2022, and the first patient was enrolled in ANT-007 in May 2022. An independent program-wide DMC will provide oversight of the safety of study participants.

1.2.3 Summary of clinical experience of Abelacimab

In summary, inhibiting FXI with abelacimab has the potential to be a novel anticoagulant with an improved bleeding profile over existing antithrombotic drugs that have been approved for patients with AF. The clinical data with abelacimab to date suggest that inhibition of FXI with abelacimab is safe and well-tolerated in healthy subjects as well as patients with AF and patients who have undergone TKA. Abelacimab leads to robust reductions in FXI activity and a prolongation of aPTT. Consistent with clinical results with other FXI agents, emerging data with abelacimab in the ANT-005 study suggest that these PD effects translate to clinical efficacy in terms of a reduction in VTE in patients who have undergone elective TKA.

1.3 Study purpose

The purpose of the ANT-006 study is to evaluate the bleeding profile of abelacimab relative to rivaroxaban in patients with AF at moderate-to-high risk of stroke.

2 Study objectives and endpoints

2.1 Primary objective

Objective	Endpoint(s)
• To evaluate the effect of abelacimab relative to rivaroxaban on the rate of major or clinically relevant non-major (CRNM) bleeding events	• Time to first event of composite of International Society on Thrombosis and Haemostasis (ISTH)-defined major bleeding or CRNM bleeding events

2.2 Secondary objective(s)

Objective	Endpoint(s)
• To evaluate the effect of abelacimab relative to rivaroxaban on the rate of major bleeding events	• Time to first event ISTH-defined major bleeding events
• To evaluate the effect of abelacimab relative to rivaroxaban on the rate of major or minor bleeding events	• Time to first event ISTH-defined major or minor bleeding events

2.3 Exploratory objective(s)

Objective	Endpoint(s)
• [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Objective	Endpoint(s)
• [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

3 Investigational Plan

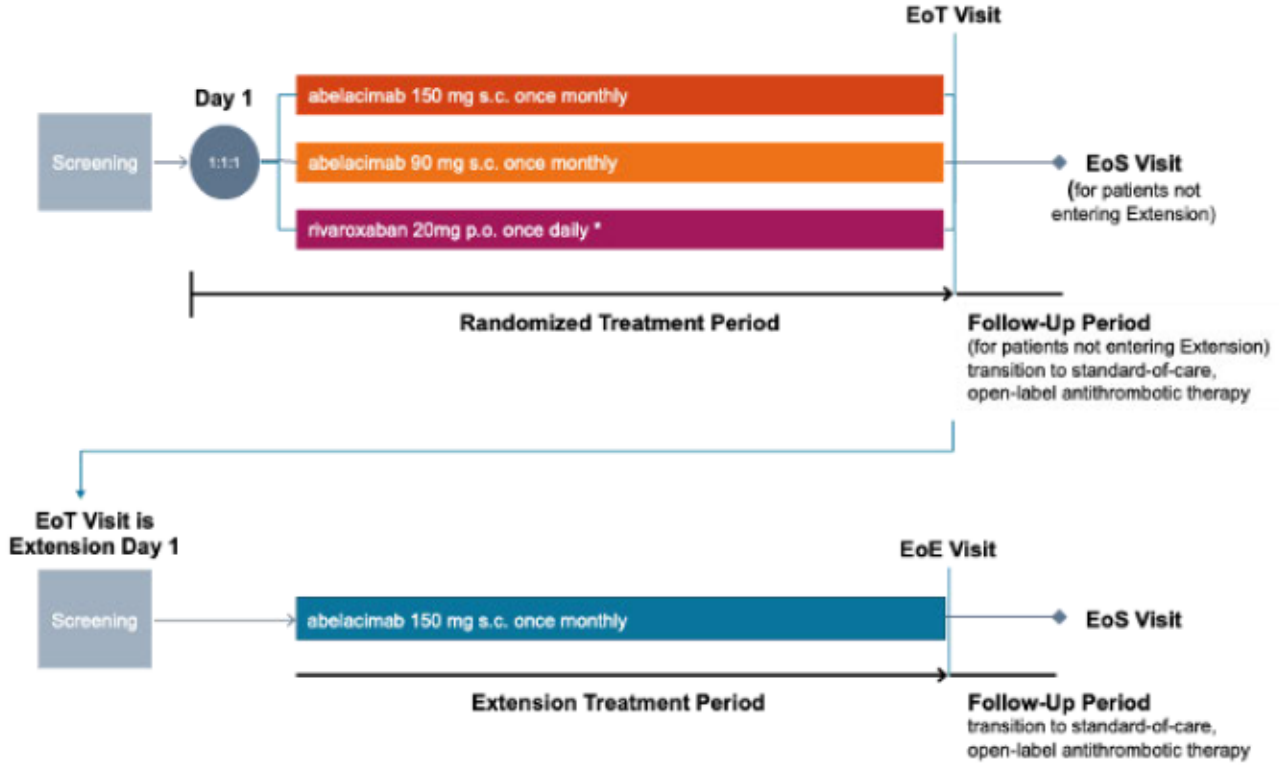
3.1 Study design

This is an event-driven, randomized, active-controlled, blinded endpoint, parallel-group study to evaluate the effect of two blinded doses of abelacimab relative to open-label rivaroxaban on the rate of major or CRNM bleeding events in patients with AF who are at moderate-to-high risk of stroke.

Randomization into treatment groups will be stratified by the use of concomitant antiplatelet use at baseline (yes/no) and renal function (CrCl ≤50 ml/min or CrCl >50 ml/min).

The study is comprised of up to 4 periods: 1) screening (up to 4 weeks), 2) study drug treatment period through the end of treatment period (EoT) visit, 3) an optional extension period beginning at the EoT visit for qualifying patients to receive open-label abelacimab treatment, and 4) transition period to appropriate standard of care antithrombotic therapy per the discretion of the investigator through the End of Study (EoS) visit.

Figure 3-1 Study design



EoT = End of Treatment
EoS = End of Study
EoE = End of Extension Treatment

* rivaroxaban patients with CrCl ≤ 50 ml/min will receive the 15 mg dose

3.1.1 Screening period

During the Screening Period (Day -30 to Day -1), all screening assessments will be completed, and the investigator will determine whether the patient is eligible for the study.

Patients entering the extension period should have eligibility confirmed per Section 4.3 and 4.4 at any time between the monthly visit prior to EoT and the actual EoT/Extension Day 1 visit.

See Section 5.2 for further details on screening and re-screening.

3.1.2 Randomization and treatment

Investigators should take measures to minimize the duration of time from when the patient is screened until determined to be eligible for randomization into the study. Eligible patients who are not on oral anticoagulation at screening should be randomized as soon as possible into the study and begin their assigned study drug on Day 1.

Patients who meet all study entry criteria but are on oral anticoagulation therapy at screening will be transitioned from their baseline anticoagulant therapy prior to being randomized and receive the first administration of study drug on Day 1 according to the guidelines in Table 3-1.

Similarly, patients receiving rivaroxaban in the Randomized Treatment Period and entering the

Extension Period should transition according to the guidelines in Table 3-1.

Table 3-1 Transition Guidelines

Baseline anticoagulant therapy	Instructions
Direct oral anticoagulant (DOAC)	The patient's last dose of DOAC should be approximately 12-24 hours prior to receiving study medication on Day 1.
Vitamin K antagonist (VKA)	After enrolled and found to be eligible, patients should have their VKA discontinued, and INRs should then be performed every 1 to 2 days based on initial INR. The patient should be randomized as soon as possible (ideally within 36 hours) once the INR is <2.5. Sites may collect repeat INR samples using point of care devices or send for local analysis, in which case results will remain as part of source documentation only.

Eligible patients will be randomized into one of the following treatment groups:

- Treatment group 1: abelacimab 90 mg s.c. monthly
- Treatment group 2: abelacimab 150 mg s.c. monthly
- Treatment group 3: rivaroxaban 20 mg p.o. once per day with the evening meal

  [Note: Patients with a CrCl ≤50 ml/min by the Cockcroft-Gault equation will receive the 15 mg p.o. daily dose of rivaroxaban]

Patients will be randomized on Day 1, which will be the date of the first administration of study drug. Patients will be contacted by phone on Day 8 for a general health and safety check. Patients will be assessed for AEs and changes in concomitant medication every month during the study treatment period; patients assigned to abelacimab will receive their s.c. injection and patients assigned to rivaroxaban will have study medication compliance assessed during these monthly visits. Every third month, these visits will include additional safety assessments and collection of blood samples for laboratory analysis.

Where permitted, visits as indicated in the Assessment Schedule (Appendix 3), may be conducted at home by staff qualified to administer s.c. injections or by telephone/video-call, depending on treatment arm. In the case of visits conducted in the patient's home, with the patient's consent, the Investigator and/or delegated staff will arrange for the service and will provide the patient's name and address to the personnel conducting the in-home visit, which will be either site staff or locally contracted agency staff.

Since this is an event-driven study, the duration of treatment for a given participant in the study will depend on the rate of accrual of major and CRNM bleeding events. As a result, the time on study drug will vary from patient to patient, depending on when the patient enrolls in relation to the EoT visit for each patient. Based on event rates in similar trials, the estimated duration of the study is expected to be approximately 27 months, but this may take longer depending on the rate of patient recruitment and clinical endpoint event rates (Patel et al 2011).

If a patient has what is expected to be a permanent discontinuation of study drug, the patient should complete the visit procedures as indicated in the Permanent Study Drug Discontinuation (PSDD) visit. Refer to Section 6.6 for more details.

3.1.3 Optional Extension Period

In order to provide longer-term data, an optional open-label extension period may be opened by the Sponsor if the DMC stops the study prematurely due to an imbalance of bleeding

substantially favoring abelacimab over rivaroxaban, and benefit:risk clearly favors abelacimab. The investigative site has the option of participating or not participating in the extension period. Patients who complete the EoT visit on study treatment and meet the eligibility criteria for the extension period may participate (see Section 4.3 and 4.4).

The EoT visit will serve as Day 1 of the extension period.

[redacted]

3.1.4 End of Treatment (EoT), End of Extension treatment (EoE) and End of Study (EoS)

When the prespecified number of adjudicated clinical endpoint events have been reached or the study is stopped early on the basis of a recommendation from the DMC, sites will be notified by the Sponsor's Clinical Study Team to schedule each patient for their EoT visit.

If the extension period has been opened and a patient is eligible to participate, the EoT visit will serve as Day 1 of the extension period (Section 3.1.4). Patients completing the extension period will have an end of extension treatment (EoE) visit (Figure 3-1).

As part of the EoT/EoE, the Investigator will make arrangements to initiate transitioning the patient to appropriate standard-of-care anticoagulation therapy following the guidelines in Section 7.1. The patient may be asked to complete an optional patient experience survey as part of the EoT visit. A minimum of 4-weeks after the EoT/EoE visit or after the patient has started their SoC anticoagulation therapy (whichever is longer), a follow-up visit either by telephone/video-call or in-person will be considered the EoS visit.

3.1.5 Study Steering Committee

A Study Steering Committee (SSC), led by the Thrombolysis in Myocardial Infarction (TIMI) Study Group, an Academic Research Organization at Brigham and Women's Hospital and Harvard Medical School, along with the Sponsor, will have overall responsibility for the conduct and supervision of the study. The SSC will make all final recommendations to the Sponsor regarding trial status (e.g., modification or stopping).

The SSC, along with the Sponsor, will be primarily responsible for the creation, review, and submission of publications and presentations related to the study and any approved sub-studies or ancillary analyses after completion of the study. Any materials or publications must be submitted to the Sponsor for review and comment prior to publication or public dissemination.

Further details of the composition, roles, responsibilities, and processes of the SSC will be documented in the SSC Charter.

3.1.6 Clinical Events Committee

A Clinical Events Committee (CEC) will review and adjudicate key endpoint events including deaths, suspected strokes/transient ischemic attacks (TIAs), suspected systemic embolic events, suspected myocardial infarctions (MI), suspected venous thromboembolism (VTE) events and overt bleeding events.

CEC members will be blinded to all treatment assignments. The CEC-adjudicated data will be used in the final safety and efficacy analyses.

During the extension period, bleeding, cerebrovascular, and systemic embolic endpoint events will be centrally reviewed and classified by the CEC.

Further details of the composition, roles, responsibilities, and processes of the CEC during the randomized and extension periods will be documented in the CEC Charter.

3.1.7 Independent Data Monitoring Committee

An independent DMC will monitor the progress of the study and ensure that the safety of patients in the study is not compromised. The DMC will review accumulating data on a regular basis and will have access to unblinded data. Based on review of safety events and, in particular, bleeding events, the DMC will make recommendations to the SSC on the continuation of the study. In particular, the DMC may advise the SSC on an imbalance of bleeding substantially favoring abelacimab over rivaroxaban and a benefit:risk clearly favoring abelacimab as described in Section 3.1.3. The DMC may also recommend changes to the protocol to ensure the safety of trial patients or may recommend early termination of the study to the SSC. DMC oversight will continue during the extension period.

Further details of the composition, roles, responsibilities, and processes of the DMC will be documented in the DMC Charter.

3.2 Rationale for study design

The primary objective of this study is to evaluate the bleeding profile of abelacimab relative to rivaroxaban in patients with AF at moderate-to-high risk of stroke.

Rationale and justification for the key elements of the study design are as follows:

- **Randomization**: This decreases the chance of an imbalance in patient characteristics between treatment groups.
- **Stratification**: Randomized patients will be stratified into treatment groups according to their concomitant use of antiplatelet medications at baseline and renal function since these factors may influence the underlying bleeding risk in patients.
- **Blinding**: The study will be open-label with respect to abelacimab vs. rivaroxaban; however, investigators and patients randomized to abelacimab will be blinded to the abelacimab dose. This design allows more simplicity in the conduct of the trial and decreases the patient's burden by eliminating the need to receive placebo injections of the study drug in patients randomized to rivaroxaban or the need to take a daily placebo in patients randomized to abelacimab.
  Bias will be avoided by following strict randomization procedures and having study endpoints adjudicated by an independent CEC comprised of qualified experts who will adjudicate events in accordance with endpoint evaluation guidelines.
- **Active control:** Provides a comparison group for safety, tolerability, and efficacy endpoints.

The patient population will be described in more detail in Section 4 below.

3.3 Rationale for dose/regimen

The abelacimab 90 mg and 150 mg doses were selected for this study because they are likely to bracket the efficacious dose range based on the available preclinical, genetic, and clinical studies. Preclinical studies suggest that FXI inhibition of 50% or more may result in a lower incidence of VTE (Crosby et al 2013). Human genetic epidemiology data meanwhile suggest that reducing FXI levels by 80% or more are associated with a reduced incidence of stroke and

VTE (Salomon et al 2008, Salomon et al 2011, Preis et al 2017). In clinical studies of agents that target FXI, FXI reduction by approximately 50% with either a FXI-ASO or a monoclonal antibody directed against FXIa were associated with similar antithrombotic efficacy to enoxaparin, while inhibition of FXI by approximately 80% or more was associated with superior antithrombotic efficacy compared to enoxaparin in patients undergoing elective TKA (Büller et al 2015; Weitz et al 2020).

[redacted]

[redacted]

The DMC will only recommend proceeding to the extension if the safety and benefit:risk of the 150 mg dose of abelacimab is favorable as compared to rivaroxaban. This dose recapitulates what is seen in patients with severe Factor XI deficiency and is the dose being investigated in several ongoing Phase 3 pivotal trials. Patients who were randomized to the 150 mg dose will remain on that dose. [redacted]

3.4 Rationale for choice of comparator

Rivaroxaban, a direct factor Xa inhibitor, will be the comparator anticoagulant agent in this study. Historically, warfarin has been the standard of care anticoagulant for patients with AF. Warfarin, however, has a narrow therapeutic range, requires frequent laboratory monitoring, and is commonly not used in higher risk AF patients due to the risk of bleeding. By contrast, rivaroxaban is one of the most widely used DOACs and does not require regular laboratory monitoring.

Rivaroxaban has been approved for the reduction of stroke and systemic embolism in AF. Rivaroxaban was demonstrated to be non-inferior to warfarin in reducing the risk of stroke and systemic embolism and was not significantly different from warfarin in the incidence of major or clinically relevant non-major bleeding events in the ROCKET-AF study (Patel et al 2011). Compared to warfarin, patients receiving rivaroxaban had significantly lower rates of intracranial hemorrhage and fatal bleeding events.

3.5 Rationale for Extension Period

The extension period will provide the opportunity to collect long-term data on abelacimab use and allow patients access to abelacimab prior to its marketing authorization.

4 Population

Approximately 1200 patients with AF at moderate-to-high risk of stroke in whom anticoagulation therapy is indicated and planned for the duration of the study will be randomized.

4.1 Inclusion criteria

Patients eligible for inclusion in this study must fulfill all the following criteria:

1. Able to provide written informed consent before any study assessment is performed
2. Male and female patients ≥ 55 years old
3. History of AF or atrial flutter with planned indefinite anticoagulation. Patients with newly diagnosed AF are eligible.
4. A CHA_2DS_2-VASc of ≥4 OR
   A CHA_2DS_2-VASc of ≥3 with at least 1 of the following:
   a. Planned concomitant use of antiplatelet medication use (i.e., aspirin and/or P2Y12 inhibitor) for the duration of the trial
   b. CrCl ≤50 ml/min by the Cockcroft-Gault equation (see Section 5.3.3)

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study:

1. Use of other investigational drugs within 5 half-lives prior to enrollment or until the expected pharmacodynamic effect has returned to baseline, whichever is longer
2. History of hypersensitivity to any of the study drugs (including rivaroxaban) or its excipients, to drugs of similar chemical classes, or any contraindication listed in the label for rivaroxaban (See Section 6.7.1 for examples)
3. Patients with an intracranial or intraocular bleed within the 3 months prior to screening
4. Clinically significant mitral stenosis (valve area <1.5 cm2)
5. Mechanical heart valve or other indication for anticoagulation therapy other than atrial fibrillation (e.g., venous thromboembolism)
6. Known presence of an atrial myxoma or left ventricular thrombus
7. History of left atrial appendage closure or removal
8. Active endocarditis
9. Systolic BP >180 mm Hg or diastolic BP >100 mm Hg on repeated measurements at screening
10. Planned invasive procedure with potential for uncontrolled bleeding (e.g., major surgery)
11. Any stroke within 14 days before randomization or TIA within 3 days before randomization
12. A CrCl <15 mL/min or on dialysis at the time of Screening
13. Platelet count ≤70,000/mm^3 at the Screening Visit
14. Hemoglobin <8 g/dL at the Screening Visit
15. aPTT or PT >1.5x the upper limit of normal (ULN) at the Screening Visit, if the patient is not on an anticoagulant
16. Women of child-bearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, unless they agree to use highly effective methods of contraception during their participation in the trial and for at least 10 weeks after the last dose of abelacimab for women randomized to abelacimab. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). 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 patients in the study, the vasectomized male partner should be the sole partner for that patient
- 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. Hormonal contraceptive methods should not be used or encouraged if considered to be contraindicated. 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 reported menopausal status or oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment with follicle stimulating hormone (FSH) is she considered not of child-bearing potential.

17. Sexually active males with female partners who are WOCBP must agree to use a condom or use other reliable birth control methods during their time in the study and should not father a child or donate sperm during the study period
18. History of drug addiction or alcohol abuse in the past 2 years, as judged by the Investigator
19. Significant illness which has not resolved within two (2) weeks prior to the start of the study drug
20. Any medical or psychiatric condition which in the judgment of the Investigator may preclude patients of complying with study requirements for the duration of the study

4.3 Extension period inclusion criteria

Patients eligible for inclusion in the extension period must fulfill all the following criteria:

1. Ongoing study treatment for the randomized part of the trial at the EoT visit
2. Able to provide written informed consent to enter the extension period

4.4 Extension period exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in the extension period:

1. History of hypersensitivity to abelacimab
2. Patients with an intracranial or intraocular bleed within the 3 months prior to EoT
3. Clinically significant mitral stenosis (valve area <1.5 cm2)
4. Mechanical heart valve or other indication for anticoagulation therapy other than atrial fibrillation (e.g., venous thromboembolism)
5. Known presence of an atrial myxoma or left ventricular thrombus
6. History of left atrial appendage closure or removal
7. Active endocarditis
8. Systolic BP >180 mm Hg or diastolic BP >100 mm Hg on repeated measurements
9. Planned invasive procedure with potential for uncontrolled bleeding (e.g. major surgery)

10. Any stroke within 14 days before EoT or TIA within 3 days before EoT
11. Platelet count ≤70,000/mm3
12. Hemoglobin <8 g/dL
13. Women of child-bearing potential (WOCBP) as described in Section 4.2.
14. Sexually active males with female partners who are WOCBP must agree to use a condom or use other reliable birth control methods during their time in the study and should not father a child or donate sperm during the study period
15. History of drug addiction or alcohol abuse in the past 2 years, as judged by the Investigator
16. Significant illness which has not resolved within two (2) weeks prior to the EoT
17. Any medical or psychiatric condition which in the judgment of the Investigator may preclude patients of complying with study requirements for the duration of the study

5 Procedures and assessments

Patients should be seen for all visits/assessments as outlined in the Assessment Schedule (Appendix 3) within the permitted visit windows. All randomized patients will be followed until the EoS visit, even if they prematurely discontinued study drug (see Section 6.5).

5.1 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation) Institutional Review Board (IRB) or Ethics Committee (EC)-approved informed consent.

Anthos Therapeutics or a delegate on their behalf will provide to investigators a proposed informed consent form (ICF) that complies with the ICH E6 Good Clinical Practice (GCP) guideline and regulatory requirements and is considered appropriate for this study. The ICF also includes a section related to optional future research which will require a separate signature if the patient agrees to future research. Any changes to the proposed consent form suggested by the Investigator must be agreed to by Anthos Therapeutics before submission to the IRB or EC.

Information about common side effects already known about the investigational drug can be found in the IB. Information about common side effects already known about rivaroxaban can be found in the Summary of Product Characteristics [Xarelto® (rivaroxaban) SmPC] and Prescribing Information [Xarelto® (rivaroxaban) – Package Insert]. This information is included in the patient informed consent and should be discussed with the patient 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 which results in an update to the informed consent must be discussed with the patient.

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

A separate optional consent form for the collection of [redacted] will also be offered to patients.

A copy of the approved version of all consent forms must be provided to the [redacted] after IRB/EC approval.

5.2 Patient screening

During the screening period, patients will undergo a medical history and physical examination including collection of vital signs and a 12-lead ECG. Blood and urine samples will be taken for clinical laboratory testing and other screening assessments. If a screening laboratory result is outside eligibility requirements, those laboratory tests which did not meet eligibility criteria may be re-tested. All results must be available prior to randomization for the patient to be enrolled in the study.

In general, it is permissible to re-screen a patient if s/he fails the initial Screening or falls out of the screening window timelines. A new screening number will be assigned to a patient who is re-screened, thus no screening number will be used twice. Re-testing of laboratory tests, which did not meet eligibility criteria, within the screening window does not constitute re-screening as it is permitted within a screening window.

Reasons for screen failure will be documented in the site log. Additionally, demographic data, reason for screen failure (inclusion/exclusion) and serious adverse event (SAE) data - as applicable - will be collected in the clinical database from patients who are considered screen failures. Adverse events from screen failures, which are not considered to be SAEs, will be followed by the investigator and collected only in the source data.

For any questions about patient eligibility or screening procedures, the investigator is encouraged to contact [redacted]

5.2.1 Patient demographics/other baseline characteristics

Demographic and baseline characteristic data will be collected on all randomized patients. Relevant medical history/current medical conditions and concomitant medications present before signing of the informed consent will also be recorded.

Investigators have the discretion to record abnormal test findings on the medical history electronic case report form (eCRF), if in their judgment, the test abnormality was present prior to the informed consent signature.

Baseline CHA_2DS_2-VASc score components and anticoagulant-naïve status will be collected in the clinical database. For the purposes of this study, a patient will be considered anticoagulant-naïve if, in their medical history, they have not been treated with anticoagulant therapy, e.g., VKA, DOAC, or parenteral anticoagulant therapy, for more than 60 continuous days at any time.

5.2.2 Height and weight

Height in centimeters (cm) and body weight [to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes] will be measured as part of the physical examination at the screening visit.

BMI will be calculated by the EDC system using the following formula:

$$\text{BMI} = \text{Body weight (kg)} / [\text{Height (m)}]^2$$

BMI results will be documented in the eCRF to 2 decimal places.

5.2.3 Hepatitis screen, HIV screen

All patients will be screened for HIV, Hepatitis B and C. In the event a patient is re-screened, these tests do not have to be repeated.

5.3 Baseline Safety

5.3.1 Physical examination

A physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, musculoskeletal, vascular, and neurological.

Information from all physical examinations must be recorded as a part of source documentation at the study site. Significant findings that were present prior to the patient signing the informed consent will be documented in the Medical History part of the eCRF. Significant findings made after starting the study drug, which meet the definition of an AE will be recorded on the AE section of the eCRF.

5.3.2 Vital signs

Vital signs will include the collection of body temperature (recorded in °C), blood pressure (BP) and pulse measurements.

5.3.3 Laboratory evaluations

Details regarding collection methods and processing are outlined in the Central Laboratory Manual. During the extension period, all safety laboratory evaluations will be performed locally.

Clinically relevant deviations of laboratory test results occurring during or at completion of the study 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.

Clinically significant abnormalities must be recorded on the relevant section of the eCRFs capturing Medical history/Current medical conditions/AEs.

Hematology

Hemoglobin, hematocrit, red blood cell (RBC) count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), 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/HCO3, AST, ALT, glucose, total cholesterol, and triglycerides will be measured. If the total bilirubin concentration is >2x the ULN, direct and indirect reacting bilirubin should be differentiated.

For the purposes of this study, creatinine clearance (CrCl) will be estimated by the Cockcroft-Gault equation as follows:

$$\text{CrCl (ml/min)} = \frac{(140 - \text{age}) \text{ x weight (kg)}}{72 \text{ x serum Creatinine (mg/dL)}} \text{ x } 0.85 \ (if \ female)$$

Coagulation profile

Samples for standard aPTT as well as PT/INR will be collected at the visits noted in the assessment schedule. The results of these tests will be blinded to site staff during the treatment period, but available during the screening and post-treatment follow up period.

Urinalysis

Urine will be collected for 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.

5.3.4 Electrocardiogram (ECG)

ECGs must be collected, interpreted locally by a qualified physician, appropriately signed, and archived at the study site.

5.3.5 Pregnancy and assessments of fertility

All female study participants will have serum pregnancy testing at screening. Women who are post-menopausal or who have had oophorectomy without hysterectomy will have hormonal status confirmed at screening by FSH.

Female study participants who are considered to be WOCBP after the screening period will continue to have local urine pregnancy testing throughout the study as per the Assessment Schedule (Appendix 3); additional pregnancy testing may be performed to meet local requirements. Patients will not receive study medication if the results of the pregnancy test are positive.

5.4 Clinical Endpoints

5.4.1 Bleeding

All suspected bleeding events either reported by the subject or observed by the Investigator should be recorded.

Overt bleeding events will be adjudicated and/or classified by an independent and blinded CEC (Section 3.1.6). The CEC will classify bleeding events in accordance with the International Society on Thrombosis and Haemostasis (ISTH) definitions and guidance (Kaatz et al 2015). The definitions will be detailed in the CEC Charter.

The details of all reported bleeding events will be submitted to the CEC as described in the endpoint reporting guidelines. These details may include, but are not limited to,

- Location of the bleeding
- Duration of the bleeding
- Treatment of the bleeding event including notes or summaries of recommendations from a healthcare professional from whom medical treatment was obtained such as otolaryngology consults for ear, nose, or throat bleeds; urology consults for hematuria or urogenital tract bleeds; surgical consults for skin, soft tissue, or internal bleeds;

gynecology consults for uterine or vaginal bleeds; neurology or neurosurgical consults for intracranial bleeds; or ophthalmology consults for ocular bleeds

- Number of blood product transfusions
- Magnitude of the bleeding (e.g., size if skin or subcutaneous hematoma)
- Hemoglobin (Hb) levels at the time of the bleeding event, lowest value, pre- and post-transfusion values, and after resolution of the bleeding event
- Any diagnostic tests done to evaluate the bleeding such as endoscopy for gastrointestinal (GI) bleeds
- Any diagnostic imaging, e.g., x-ray, computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound, performed to evaluate the bleeding
- Any other information that could be of help to the CEC in adjudicating the bleeding event.

Endpoint Reporting Guidelines will provide detailed instructions for sites on the documentation, data collection, and reporting required for each suspected bleeding event.

5.4.2 Efficacy

The independent and blinded CEC will adjudicate and classify the following events:

- Ischemic stroke
- Transient ischemic attack (TIA)
- Non-CNS (systemic) arterial embolic events
- Myocardial infarction (MI)
- Venous thromboembolism (VTE) events
- Death

Adjudicated results will be used for the final analysis. Definitions and further details will be documented in the CEC charter.

5.5 Other assessments

5.5.1 Pharmacokinetics

Blood samples for PK will be collected before administration of study drug on study visits as defined in the Assessment Schedule (Appendix 3). Concentrations of plasma total abelacimab (i.e., abelacimab 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 abelacimab 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.

Follow instructions outlined in the Central Laboratory Manual regarding sample collection, numbering, processing, and shipment.

5.5.2 Pharmacodynamic assessments

PD samples will be collected at the timepoints defined in the assessment schedule. Instructions for bio-sample processing will be contained in the Central Laboratory Manual regarding sample collection, numbering, processing, and shipment.

PD Biomarkers including but not limited to the following may be studied:

- Free FXI – FXI that is not bound to abelacimab will be measured in plasma
- Total FXI – FXI that is either bound to abelacimab or free will be measured in plasma
- aPTT

[redacted]

A detailed description of the assay methods will be included in the Bioanalytical Data Report.

5.5.3 Immunogenicity

An immunoassay-based method will be used to detect anti-abelacimab anti-drug antibodies (ADAs). The analytical method will be described in detail in the IG Bioanalytical Data Report. IG samples will be collected before administration of study drug on study visits as defined in the Assessment schedule (Appendix 3).

Follow instructions outlined in the Central Laboratory Manual regarding sample collection, numbering, processing, and shipment.

5.5.4 Additional biomarkers (blood)

Additional blood samples will be collected at timepoints defined in the Assessment schedule and banked for potential future exploratory analysis (Appendix 3).
Additional biomarkers may include, but are not necessarily limited to:

- [redacted]

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. This may be conducted in a subset of patients.

5.5.5 [redacted]

[redacted]

[redacted]

5.5.6 [redacted]

[redacted]

5.6 [redacted]

[redacted]

6 Treatment

6.1 Study treatment

For more details please refer to the Pharmacy Manual.

6.1.1 Abelacimab (MAA868)

Anthos Therapeutics, or a delegate working on their behalf, will provide Abelacimab [redacted] Details on the requirements for storage and management of study treatment, and instructions to be followed for study treatment preparation and administration are outlined in the Pharmacy Manual.

6.1.2 Rivaroxaban

Rivaroxaban 15 mg and 20 mg will be provided as commercially available film-coated tablets. Storage conditions described on the label must be followed.

6.1.3 Additional study treatment

No additional treatment beyond investigational drug and rivaroxaban are included in this trial.

6.2 Treatment assignment and randomization

Patients will be randomized on Day 1 to one of the following treatment arms in a 1:1:1 ratio:

- Abelacimab (MAA868) 90 mg s.c. monthly
- Abelacimab (MAA868) 150 mg s.c. monthly
- Rivaroxaban 20 mg p.o. once per day with evening meal

[Note: Patients with a CrCl ≤50 ml/min by the Cockcroft-Gault equation will have a dose adaptation to rivaroxaban 15 mg p.o. daily.]

Randomization into treatment groups will be stratified by the use of concomitant antiplatelet use at baseline (yes/no) and renal function (CrCl ≤50 ml/min or CrCl >50 ml/min). Patients randomized to the rivaroxaban arm may be dose adjusted between the 15 mg dose and 20 mg doses depending on CrCl values.

Once a subject is stratified and randomized, the subject will stay in that starting stratum, randomized treatment group, and treatment regimen for analyses purposes even if their dose is subsequently adjusted.

Once Investigators have ascertained that the patient is eligible for the study, they will contact the Interactive Web or Voice Response System (IxRS) before the first administration of study drug. The IxRS will require the following information in order to randomize a patient to the correct stratification: year of birth, CrCl (Cockcroft-Gault) and whether the patient takes antiplatelet medications (i.e., aspirin and/or a P2Y12 inhibitor) as a concomitant medication. The IxRS will allocate the treatment group assignment for the patient.

Emergency unblinding will be done through the IxRS system. The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment assignment. The decision of whether or not to unblind lies with the investigator and it is the sole responsibility of the investigator to determine the need for immediate unblinding. However, if time and circumstances permit, the Investigator is encouraged to contact the [redacted]

The specifications for generation of the randomization schedule will be prepared by the study biostatistician and the contract research organization (CRO) in charge of the IxRS. An independent biostatistician, not otherwise part of the clinical study execution team, will generate the randomization schedule. The randomization numbers will be generated to ensure that treatment assignment is unbiased.

6.3 Treatment blinding

Patients, Investigators, and Sponsor staff directly involved in the study may be aware of the treatment assignment between abelacimab and rivaroxaban but will remain blinded to the dose of abelacimab assigned. An independent DMC will monitor the data (AEs, SAEs, bleeding events, stroke, systemic embolic events, and death) in an unblinded manner on a periodic basis. An independent statistical group, not otherwise involved in the study, will prepare and provide the required reports to the DMC as per the DMC Charter.

The study's primary safety and efficacy endpoints will be adjudicated by the CEC whose members will remain blinded to treatment assignment.

Administration of study treatment during the extension period will be open-label.

6.4 Treating the patient

6.4.1 Dispensing the study drug Abelacimab

Each study site will be supplied with abelacimab as single-use vials via the IxRS system. A unique kit number is printed on the vial label which corresponds to the abelacimab treatment

arm. Investigator staff will identify the study drug vial to be used for the patient by contacting the IxRS and obtaining the kit number containing that vial.

At the Day 1 and Day 30 visits, abelacimab will be administered to the patient by qualified medical personnel at the study center via s.c. injection as specified in the Pharmacy Manual. For these first two doses, patients must remain at the study center for at least 1 hour after administration of study drug to monitor for any ISRs, hypersensitivity reactions, or other AEs. Starting with the third dose, patients will either return to the study center every month to receive s.c. administration of study drug or opt to have study drug administered outside the study center by a visiting nurse or other assigned individual qualified to administer s.c. study medication (or a combination of visit scenarios depending on patient and site availability).

Patients participating in the extension period that received rivaroxaban or abelacimab 90 mg in the randomized period should be monitored as described above after the first dose of abelacimab 150 mg.

6.4.2 Rivaroxaban

Each study site will be supplied with cartons of rivaroxaban 20 mg tablets and 15 mg tablets via the IxRS system. On Day 1, patients assigned to rivaroxaban will be given a supply of rivaroxaban and will be instructed to take the first dose that evening with food. Throughout the study, rivaroxaban will be dispensed at appropriate intervals to ensure patients have adequate quantities of study drug between study visits.

In case of circumstances preventing a patient from attending on-site visits, sites may, with the patient's consent, arrange the shipment of rivaroxaban directly to the patient's home as permitted by local regulations. In this case, the Investigator and/or delegated staff will arrange for the courier service and will provide the patient's name and shipping address to the courier.

6.4.3 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol.

Study medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the patient except for the kit number. The labels will have an open field for sites to write in the patient's randomization number for reconciliation purposes.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial.

At the conclusion of the study, and as appropriate during the course of the study (only after instructed to do so), the investigator will either locally destroy the unused study treatment (if local SOPs permit) or return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the [redacted] monitor to arrange for destruction.

6.4.4 Instructions for administering study treatment

Abelacimab injection will be prepared by the Pharmacist or qualified designated site staff according to instructions in the Pharmacy Manual and administered subcutaneously.

Rivaroxaban will be self-administered by the patient.

6.4.5 Method of assessing treatment compliance

The investigator should promote compliance with study medications by instructing the patient to take the study treatment exactly as instructed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as instructed.

Patients assigned to rivaroxaban will be asked to bring all used and unused study drug containers to every visit, including remote (video-call) visits as applicable. Compliance will be assessed at each visit by means of tablet counts and documented on the relevant eCRF page.

6.5 Study treatment interruptions

Study drug may be interrupted at the Investigator's discretion for medical or surgical reasons.

Reasons for temporary study drug interruption may include a planned invasive procedure or surgery for which one would typically stop oral anticoagulation (see Section 6.5.2); clinical indication for a prohibited medication (see Section 6.7.1); a bleeding AE (see Section 8.2); or any other medical condition where the Investigator judges that it is the in the best interests of the patient to temporarily interrupt study drug.

Since patients with AF are at underlying risk of stroke and systemic embolism, the duration of any study drug interruption should be kept to the minimum possible unless there is a contraindication to anticoagulation. Patients who have interrupted study drug should be re-evaluated regularly by the Investigator to determine the risks and benefits of resuming study drug.

For patients assigned to rivaroxaban, the eCRF page for study drug interruption should be completed for any temporary study treatment interruptions of 2 or more consecutive days and include the date/time of the last dose, the reason for the temporary interruption (e.g., procedures), and other required details.

For patients assigned to abelacimab, the eCRF for study drug interruption is required for any missed study treatment >45 days from the previous dose and include the date/time of the last dose, the reason for the temporary interruption (e.g., procedures), and other required details.

There is no limit on either the number of study drug temporary interruptions or the maximum length of a study drug temporary interruption. As long as the study has not completed, a patient who has interrupted study drug can resume study drug as soon as it is determined to be appropriate by the Investigator.

A patient who continues to be on study treatment interruption when the randomized period of the study has completed will be considered to have permanently discontinued study drug, will not be eligible for the extension and should complete a PSDD visit and a EoS visit approximately 30 days later (see Section 6.6).

Investigators are strongly encouraged to call the [redacted]

6.5.1 Follow-up of patients with Study Treatment Interruptions

All patients who temporarily interrupt study drug should continue to be followed. During study

drug temporary interruptions, patients will be followed for SAEs and endpoints by telephone contact (or visit if necessary) approximately once a month until study drug treatment is resumed along with regularly scheduled protocol-specified visits.

If a patient temporarily interrupts study drug due to an AE, the Investigator will attempt to follow the event until it has resolved or stabilized. If the patient and Investigator agree that study drug can be resumed without increased risk to the patient, study drug may be resumed at any time.

6.5.2 Study treatment interruptions for invasive procedures

During their participation in the study, patients may need to undergo an invasive procedure/surgery. The peri-procedural management of study drug anticoagulation will vary depending on the type and timing (elective, urgent, or emergent) of procedure/surgery, the assigned treatment arm, and a consideration of the patient's risk of hemorrhage versus the patient's risk of stroke and systemic embolism. Detailed recommendations are provided in a Periprocedural Guidance Document. Investigators are strongly encouraged to contact the [redacted] for guidance with regards to whether study drug interruption is recommended for a given procedure/surgery.

In the event of an urgent/emergent procedure, investigators are strongly encouraged to contact the [redacted] for guidance with regards to reversal strategies.

Local aPTT results prior to any invasive procedure/surgery should be saved along with procedure/operative reports as source documents.

After completion of the procedure/surgery and when hemostasis has been achieved, the short-term use of parenteral anticoagulation or oral anticoagulation is permitted until the patient can be seen in the study center and resume study drug.

6.6 Permanent study drug discontinuation

Permanent study drug discontinuation (PSDD) is allowed at the Investigator's discretion or patient's request at any time. The Investigator should call the [redacted] in case of potential PSDDs.

If a patient has what is expected to be a permanent discontinuation of study drug, the patient should complete PSDD visit procedures outlined in the Assessment Schedule (Appendix 3). At the PSDD visit, unless the patient has a contraindication to anticoagulation, Investigators should arrange patients to be transitioned to appropriate SoC anticoagulation therapy minimizing any gap in anticoagulation since patients with AF are at underlying risk of stroke and systemic embolism (see Section 7.1).

Patients who permanently discontinue study drug will have an EoS visit approximately 30 days after the PSDD visit and then will be contacted periodically, approximately every 12 weeks, by telephone for SAEs and endpoints (see Section 7.2) until the site has been notified by the SSC that the randomized period of the trial has ended at which point the patient's participation in the study can be considered completed. Sites should not enter the patient as "complete" in the eCRF until the study has been declared complete, unless the patient has withdrawn their consent to be followed by all possible methods (i.e., in person, remotely, via third party) and refuses to permit review of the medical records.

In certain situations, patients who have previously permanently discontinued study drug and had an PSDD Visit can be allowed to resume study drug. The Investigator should contact the [redacted] to determine whether or not a patient who completed a PSDD visit can resume

study drug.

Any patient who permanently discontinues study drug and also wishes to withdraw consent for participation in the study must complete the protocol-specific withdrawal of consent procedures (see Section 7.3). The Investigator should contact the [redacted] to discuss cases in which a patient wishes to withdraw before the decision is made and withdrawal procedures are begun. Withdrawal procedures can begin only after discussion and confirmation that the patient's desire to withdraw full consent.

6.7 Concomitant treatment

The Investigator must instruct the patient to notify the study staff of any new medications he/she takes after being enrolled into the study.

All prescription medications, OTC drugs including herbal supplements, 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 eCRF. Medication entries should be specific to trade and generic 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 the [redacted] during screening or, if the patient is already enrolled, to determine if the patient should continue with study treatment.

6.7.1 Prohibited medication

In case any of the following medications are clinically necessary, no further dosing of the study drug should occur until the investigator has determined that it is safe for the patient to resume study drug:

- Anticoagulants, other than the assigned study drugs, by any route
- Parenteral antiplatelet drugs (except NSAIDs)
- Thrombolytic agents.

For patients in the rivaroxaban arm: use of combined P-gp and strong CYP3A inhibitors such as atazanavir, clarithromycin, dronedarone, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole is prohibited as well as other drugs in accordance with local regulations during their time in the study.

For patients in the rivaroxaban arm: use of combined P-gp and strong CYP3A inducers such as rifampin/rifampicin, rifabutin, rifapentin, phenytoin, phenobarbital, primidone, St. John's Wort, and carbamazepine is prohibited, as well as other drugs in accordance with local regulations during their time in the study.

6.7.2 Other Prohibitions and Restrictions

- Women of childbearing potential (WOCBP) must agree to remain on an effective method of contraception during their time in the study and for at least 10 weeks after the last dose of abelacimab for WOCBP randomized to abelacimab.
- Men must agree not to father a child or donate sperm during their time in the study.

6.8 Risks and benefits

The risks and benefits of using rivaroxaban in patients with atrial fibrillation are described in the Summary of Product Characteristics [Xarelto® (rivaroxaban) SmPC] and Prescribing Information [Xarelto® (rivaroxaban) – Package Insert].

The risks associated with the use of abelacimab are those inferred by the biology of and clinical experience with abelacimab, and those associated with study procedures.

There may be unknown risks of abelacimab which may be serious and unforeseen. Refer to the IB for further details regarding risks based on experience and biology of abelacimab.

6.8.1 Risks associated with the COVID-19 pandemic

The study treatments, including abelacimab, are not expected to alter the natural defense mechanisms or developing immunity to COVID-19. Anticoagulation therapy may have beneficial effects in preventing thromboembolic complications of COVID-19.

The COVID-19 pandemic may present added challenges for trial participants who may risk exposure to COVID-19 during travel to research centers and interactions with research staff. In order to minimize risk to trial participants, only critical study tasks were maintained. Furthermore, study procedures were designed to be adaptable to changing conditions related to the COVID-19 pandemic.

Investigators should make every effort to ensure that they are following local guidelines to prevent the spread of COVID-19 as well as provide appropriate medical oversight to patients enrolled into this study, whether visits are taking place on-site or using one of the flexible options that are available including:

- In-home visits in lieu of on-site visits for the s.c. administration of abelacimab;
- remote (via telephone or video-calls) visits in lieu of on-site visits when s.c. administration of abelacimab is not required;
- IxRS dispensing of multiple months of rivaroxaban supplies rather than requiring rivaroxaban patients to return to the site to obtain these supplies every month, as well as direct-to-patient shipment (from site to patient's home) of rivaroxaban supplies as needed and locally permitted.

If a patient contracts COVID-19 while enrolled in the study, the patient should be managed according to usual medical practice. COVID-19 should be recorded in the adverse events page.

Vaccination for COVID-19 is permitted during the study course.

Patients should not receive their injection of abelacimab within 3 days of receiving a COVID-19 vaccine.

6.8.2 Risks Based on Prior Clinical Experience with Abelacimab

Abelacimab has been generally well-tolerated in the three clinical studies completed to date (CMAA868X2101, CMAA868A1101, and ANT-003) as well as in the multiple dose study in low-risk AF patients (ANT-004) and in patients undergoing elective TKA surgery (ANT-005). To date, across the Phase 1 and Phase 2 studies performed with abelacimab, more than 250 subjects have been administered abelacimab. AEs have been infrequent and well-balanced between the treatment and placebo arms. No dose-dependent safety findings have been observed. While fecal occult blood tests have been positive in a few study participants, none of these positive test results remained positive on repeat testing or were associated with any

clinical or laboratory signals indicating active bleeding. Thus, no specific risks have been identified based on prior clinical experience for abelacimab.

6.8.3 Risks based on [redacted]

[redacted]

6.8.4 Risk based on the biology of abelacimab

6.8.4.1 Bleeding risk

Since abelacimab is an inhibitor of FXI and FXIa, it acts as an anticoagulant. The bleeding risk of abelacimab in patients with AF is unknown; however, treatment with abelacimab can be expected to result in a bleeding phenotype comparable to the bleeding phenotype in patients with severe FXI deficiency.

Patients with severe FXI deficiency generally do not experience spontaneous bleeding, and spontaneous muscle or joint bleeding or intracranial bleeding events are rare (Bolton-Maggs 2000, Duga and Salomon 2013). Bleeding events that occur are often injury- or trauma-related, particularly in tissues with increased fibrinolytic activity such as the oral mucosa, nasal mucosa, and urinary tract.

An FXI-ASO was also evaluated in a FIH study in healthy subjects (Liu et al 2011) and in patients undergoing elective unilateral TKA (Büller et al 2015). Robust and sustained reductions of FXI greater than 80% for a duration exceeding 6 to 8 weeks were achieved at the highest dose with several subjects reaching undetectable levels of FXI. No bleeding occurred in subjects who received FXI-ASO in the FIH study. Furthermore, administration of FXI-ASO to patients undergoing unilateral TKA at a dose that achieved a mean 80% reduction in FXI activity appeared to be associated with a trend towards a lower incidence of major or CRNM bleeding events compared to s.c. enoxaparin (Büller et al 2015). Similar results were observed in a clinical study of a monoclonal antibody inhibitor of activated FXI, osocimab, which showed no evidence of excess risk of bleeding with osocimab in patients undergoing elective TKA (Weitz et al 2020).

In the Phase 1 studies of abelacimab (CMAA868X2101, CMAA868A1101, and ANT-003), greater than 95% inhibition of FXI was not associated with bleeding manifestations, and no clinically relevant decreases in hemoglobin or hematocrit were observed at any time-point during the study. To date, in the ANT-004 study, no major or clinically relevant non-major bleeding events have occurred with multiple s.c. administration of abelacimab; however, 1 clinically relevant bleeding event at the surgical site has been reported in a patient randomized

to abelacimab in the ANT-005 study in patients undergoing TKA.

A therapeutic strategy for the management of bleeding events in the study is provided in Section 8.2 and Appendix 2.

6.8.4.2 Potential risk associated with hypersensitivity reactions

Infusion of therapeutic proteins can result in immediate or delayed hypersensitivity reactions. Immediate reactions appear during the first hours after drug administration. Clinical presentation may include a wide of range of symptoms e.g., fever, chills, nausea, cutaneous symptoms, bronchospasm, dyspnea, dizziness, headaches, myalgia, tachycardia and/or hypotension. Anaphylaxis, urticaria, and angioedema were also reported. Delayed hypersensitivity reactions can appear between 1-2 hours and up to 14 days after administration, often with serum sickness–like symptoms (Corominas et al 2014). The incidence of hypersensitivity reactions with monoclonal antibodies (mAbs) depends on the degree of humanization, the cell line from which they were obtained and excipients. No hypersensitivity reactions were observed in the 13-week toxicity study or in the Phase 1 studies (CMAA868X2101, CMAA868A1101 and ANT-003).

Management of hypersensitivity reactions depends on the clinical presentation and severity. Treatment interruption (if applicable); fluids, vasopressors, corticosteroids, antihistamines, bronchodilators, epinephrine, and oxygen may be used, as indicated.

6.8.4.3 Potential risk associated with [redacted]

[redacted]

6.8.4.4 Potential risk associated with s.c. injection

[redacted] Injection site reactions can result in hematoma, hemorrhage, bruising, erythema, discoloration, swelling and edema formation, particularly following s.c. administration. The first and second injections of the study drug will be administered at the study site where patients will be monitored for injection site reactions.

A therapeutic strategy for the management of injection site reactions is provided in Section 8.3.

6.8.4.5 Potential risks associated with study procedures

Blood samples will be collected during the study either via venipuncture or i.v. cannula. Risks associated with blood collection include pain, swelling and/or bruising at the insertion site of the needle. Although rare, localized clot formation, infections and nerve damage may occur. Lightheadedness and/or fainting may also occur during or shortly after the blood draw.

6.8.5 Potential benefits associated with abelacimab use

FXI deficiency has been associated with a lower risk for VTE and stroke compared to the general population (Salomon et al 2008, Salomon et al 2011, Preis et al 2017). Furthermore, FXI suppression using an antisense oligonucleotide or monoclonal antibody against FXIa demonstrated a lower rate of total VTE in patients undergoing unilateral TKA with no concomitant increase in bleeding events compared to enoxaparin (Büller et al 2015; Weitz et al 2020). Preliminary data from the ANT-005 study are consistent with the results obtained with FXI-ASO and the FXIa monoclonal antibody and suggest that abelacimab has robust antithrombotic efficacy compared to enoxaparin s.c. without an increase in bleeding events.

7 Study Completion and Discontinuation

7.1 Study completion and post-study treatment

The SSC will communicate to study sites when the study is ending. Sites will be instructed to schedule an end of treatment period (EoT) visit for randomized patients or end of extension treatment (EoE) visit for extension patients, as relevant:

- Patients assigned to one of the abelacimab treatment arms should have their EoT or EoE visit scheduled approximately 30 days after their last s.c. injection of study medication.
- Patients assigned to the rivaroxaban treatment arm should complete their EoT visit starting approximately two weeks after notification from the SSC. These patients should continue to take their assigned treatment up to the day prior to the EoT visit, at which time rivaroxaban supplies must be collected.

At the EoT visit or EoE (for patients completing the extension period), all study drug supplies must be collected from the patient and the Investigator must begin plans to transition the patient to SoC anticoagulation therapy according to the guidelines in Table 7-1, unless the patient has a contraindication to anticoagulation therapy.

Table 7-1 End of Study Transition Guidelines

Transitioning to	Instructions
Direct oral anticoagulant (DOAC)	Patients should initiate oral DOAC on the same day of the EoT/EoE visit.
Vitamin K antagonist (VKA)	Patients should be given a supply of VKA and instructed to begin therapy 3 to 5 days before the EoT visit. At the EoT visit, measure PT/INR and repeat as frequently as necessary until the PT/INR is therapeutic. Sites may collect repeat INR samples using point of care devices or send for local analysis, in which case results will remain as part of source documentation only.

The EoS visit (in-person or telephone/video-call) will take place approximately 4-weeks after the EoT/EoE visit. This visit will assess patients for a general health and safety check prior to concluding their participation in the study.

7.2 Discontinuation of study treatment

Discontinuation of study treatment for a patient occurs when study drug is permanently stopped earlier than the protocol planned duration. Study drug discontinuation can be initiated by either the patient or the Investigator.

Study treatment should be discontinued from further study treatment for any of the following:

- Patient request
- The investigator judges that continued study drug administration is not in the best interest of the patient
- Pregnancy (Section 8.6)

If a patient has what is expected to be a permanent discontinuation of study drug, the patient should complete the PSDD Visit procedures (see Section 6.6).

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/video-call visits:

- signs and symptoms suggestive of bleeding, stroke, or TIA
- new/concomitant treatments
- AEs/SAEs

If the patient cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the patient, or with a person pre-designated by the patient, approximately every 12 weeks.

7.3 Withdrawal of informed consent

Patient's may voluntarily withdraw consent to participate in the study for any reason at any time. Sites should contact the [redacted]E before registering a withdrawal of consent.

Withdrawal of consent from the study can occur when a patient:

- 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 contacts, and
- does not allow analysis of already obtained biologic material which has not already been analyzed, and
- does not allow further use of already obtained biologic material for future research.

In this situation, the Investigator must make every effort (e.g., telephone, e-mail, letter) to determine the primary reason for the patient's decision to withdraw his/her consent and record this information in the eCRF and in the source document.

All effort should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in the assessment schedule (Appendix 3).

If withdrawal occurs prior to study drug dosing, study treatment must not be administered, and no further assessments conducted. The data that would have been collected at subsequent visits will be considered missing. Further attempts to contact the patient are not allowed unless safety findings require communication or follow-up.

7.4 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the Investigator should document in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. If local regulations permit, a search of local, regional, national public records, and/or internet sites may be checked to locate a patient or investigate vital status.

A patient cannot be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

7.5 Early study termination by the Sponsor

The study can be terminated by the Sponsor at any time for any reason. This may include reasons related to the benefit/risk assessment of participating in the study, practical reasons (e.g., including slow enrollment), or for regulatory or medical reasons. Should this be necessary, patients must be seen as soon as possible and treated as a prematurely withdrawn patient. 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 patient's interests. The Investigator will be responsible for informing the IRB/EC of the early termination of the trial.

8 Safety monitoring

8.1 Adverse events

An AE is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases that are present before starting study drug are only considered AEs if they worsen after starting study drug. Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

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 8.6 for an overview of the reporting requirements.

The occurrence of AEs must be sought by non-directive questioning of the patient at each visit during the study. AEs also may be detected when they are volunteered by the patient during or between visits or through physical examination finding, laboratory test finding, or other assessments. All AEs must be recorded on the Adverse Events eCRF under the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

1. the severity grade
    - mild: usually transient in nature and generally not interfering with normal activities
    - moderate: sufficient discomfort to interfere with normal activities
    - severe: prevents normal activities
2. its relationship to the study treatment
    - Related
    - Possibly related
    - Not related

3. its 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 8.4.1 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 8.4.1 for definition of SAE)
6. Its 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 patient to report any new AE (beyond the protocol observation period) that the patient, or the patient'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 [redacted]

8.2 Recommended treatment of bleeding adverse events

The management of a suspected bleeding AE is at the discretion of the Investigator and will depend on the source/location of the bleeding and the severity. In all cases of bleeding AEs, the Investigator should use clinical judgment in assessing the risk to the patient and monitor whether the bleeding is resolving or worsening. Further guidance for the management of bleeding AEs in this trial can be found in Appendix 2. Investigators are also encouraged to contact the [redacted]

All suspected bleeding events must be recorded on the appropriate eCRF page.

8.3 Recommended treatment of other adverse events

The Investigator and site staff must observe the patients for any AEs. All AEs should be treated according to clinical practice.

8.3.1 Hypersensitivity reactions

Human monoclonal antibodies such as abelacimab have a low risk of causing hypersensitivity reactions.

Hypersensitivity reactions might occur even after initial dosing. Immediate hypersensitivity reactions may appear during the first hours after drug administration; clinical presentation may

include a wide of range of symptoms, e.g., fever, chills, influenza-like syndrome, nausea, vomiting, cutaneous symptoms, bronchospasm, dyspnea, dizziness, headaches, myalgia, tachycardia, hypotension, urticaria, angioedema and acute anaphylaxis, which could be life-threatening. Delayed hypersensitivity reactions may appear between 1-2 hours and up to 14 days after administration, often with serum sickness-like symptoms.

Treatment of hypersensitivity reactions is generally symptomatic and depends on the severity of the initial reaction and the response to treatment. Antihistamines, systemic corticosteroids, and/or non-steroid ant-inflammatory drugs may be considered in milder cases of hypersensitivity reactions. Intravenous access, cardiac monitoring, high-flow oxygen, fluids, vasopressors, corticosteroids, antihistamines, bronchodilators, and epinephrine may be used in case of a serious of anaphylaxis or anaphylactoid reactions.

8.3.2 Injection site reactions

Subcutaneous injections can occasionally be associated with bruising, hematoma, and superficial vein thrombosis. Management of bruising can include resting the local area and cold compresses. Heat packs or a washcloth soaked in warm water may be applied to the bruised area for several days after the infusion or injection to promote resorption. Acetaminophen may be used to alleviate pain.

Infectious complications "cellulitis-like reactions" are usually treated with local antiseptics and may occasionally require systemic antibiotics.

Immunologic infusion site reactions could be acute, delayed or both. Clinical symptoms may include redness, swelling, induration, itching, tenderness, or pain. Immunologic infusion site reactions are usually self-limited and may be treated with cold compresses, antihistamines, acetaminophen, and topical anti-inflammatory drugs. Topical corticosteroids may be used if the reaction worsens over several days. Oral corticosteroids are seldom required.

8.4 Serious adverse event reporting

8.4.1 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 patient's general condition
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require acute medical or surgical intervention to prevent permanent impairment.

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 patient 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 patient 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 eCRF; SAEs also require individual reporting to [redacted] as per Section 8.4.2.

8.4.2 SAE reporting

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

Note: SAEs reported by patients deemed to be screen failures must be reported to [redacted]p as outlined here with appropriate information also captured in the eCRFs.

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 and whether the patient 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 [redacted] associate may urgently require further information from the Investigator for Health Authority reporting. [redacted] 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 ECs in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Clinical endpoints described in Section 5.4, such as bleeding events, ischemic stroke, hemorrhagic stroke, TIA, non-CNS systemic embolic events, venous thromboembolic events or myocardial infarction, that also meet SAE criteria will be collected as part of the endpoint

eCRF. These protocol-specific SAEs will not be reported on an individual basis in an expedited manner and instead will be adjudicated by an independent CEC. Fatal events will be reported regardless of adjudication on an aggregate basis to health authorities as required by local regulations. Other SAEs will be evaluated on a case-by-case basis to determine whether there is reasonable possibility that the study drug caused the event. If the event is considered by the sponsor or designee to meet the criteria for expedited reporting, the event will be reported in an expedited manner. Study endpoints and safety data will be regularly reviewed by an independent DMC in an unblinded manner to ensure prompt identification of any clinically concerning safety issues.

The investigator still has the responsibility to report all SAEs to the sponsor as described above.

Follow the detailed instructions regarding the submission process for reporting SAEs to [redacted] Note: SAEs must be reported to [redacted] within 24 hours of the Investigator learning of its occurrence/receiving follow-up information.

8.5 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 eCRF. Study treatment errors are only to be reported to [redacted] department if the treatment error is associated with an SAE.

All instances of misuse or abuse must be documented in the AE eCRF irrespective of the misuse/abuse being associated with an AE/SAE. In addition, all instances of misuse or abuse must be reported to the [redacted] department. As such, instances of misuse or abuse are also to be reported using the SAE form/eCRF. Table 8-1 summarizes the reporting requirements.

Table 8-1 Summary of Reporting Requirements for Medication Errors

Treatment error type	Document in Dose Administration eCRF	Document in AE eCRF	Complete SAE form/eCRF
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 8.1 and Section 8.4, respectively.

8.6 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 either of non-child-bearing potential or who have agreed to highly effective contraception as outlined in the eligibility criteria; 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 appropriate clinical follow-up for this patient and for the fetus is at the discretion of the Investigator.

To ensure patient safety, each pregnancy occurring after signing the informed consent must be **reported to** [redacted] **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 [redacted] 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.

If the Investigator becomes aware of a pregnancy occurring in the partner of a subject participating in the study, the pregnancy should be reported to [redacted] within 24 hours of becoming aware, using Pregnancy Report Form. Information regarding the pregnant partner must only be submitted after obtaining written consent from the pregnant partner. 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.

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

9 Data review and database management

9.1 Site monitoring

Before study initiation, at a (remote or in-person) site initiation visit or at an investigator's meeting, the Sponsor or Sponsor representative will review the protocol and eCRFs with the Investigator(s) and their staff. During the study [redacted] 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 patient records, the accuracy of entries on the eCRFs, 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 patient 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 eCRFs must be traceable to these source documents in the patient 's file. The Investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries [redacted] 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 eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

9.2 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 the contract research organization (CRO) working on behalf of Anthos Therapeutics. The Investigator must certify that the data entered into the Electronic Case Report Forms (eCRFs) are complete and accurate. After database lock, the Investigator will receive copies of the patient data for archiving at the investigational site.

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

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

9.3 Database management and quality control

[redacted] 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.

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.

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.

Except for the extension period, laboratory samples will be processed centrally, and the results will be sent electronically to [redacted]. During the extension period, safety laboratories will be performed locally.

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 [redacted]

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 made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Anthos Therapeutics Head of Regulatory and the Chief Medical Officer.

10 Data analysis

A general description of the statistical methods to be used to analyze this study is outlined below. Further details can be found in the Statistical Analysis Plan (SAP).

10.1 Analysis sets

- On-Treatment: will consist of all randomized patients who received at least one dose of study drug. Patients will be considered to be on-treatment if within 60 days of their last dose of study drug up to the EoT visit of the randomized treatment period.
- Intent-to-Treat (ITT): all patients randomized and dosed to be analyzed according to randomized treatment assignment. Events occurring from randomization through EoS of the randomized treatment period will be included in the analysis.
- Per Protocol: All randomized patients with a treatment compliance rate of at least 80% and do not have any major protocol violations as defined in the final SAP.
- On-Treatment Extension: will consist of all patients who received at least one dose of abelacimab in the extension period. Patients will be considered to be on-treatment if within 60 days of their last dose of study drug to the EoE visit of the extension period.

10.2 Patient demographics and other baseline characteristics

Data for background and demographic variables will be listed by treatment group and patient. Summary statistics will be provided by treatment group.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment group and patient, and summary statistics will also be provided by treatment group.

10.3 Treatments

Data for study drug administration and concomitant therapies will be listed by treatment group and patient.

10.4 Analysis of the primary variable(s)

The primary analysis will compare each abelacimab regimen with rivaroxaban for the time to first occurrence of major or CRNM bleeding in the On-Treatment Analysis Set. For each treatment regimen, the event rate will be estimated with 95% confidence intervals (CIs). The time to first event will be analyzed using the Cox proportional hazards model including treatment and the following two stratification factors as covariates:

- Planned use of concomitant antiplatelet medication use (e.g., aspirin and/or P2Y12 inhibitor) for the duration of the trial
- CrCl (Cockcroft-Gault) $\leq$ 50 ml/min

The hazard ratios (HR) with 95% CIs will be reported for both doses of abelacimab vs. rivaroxaban. A significance level of α=0.05, without adjustment for multiplicative testing, will be used. A sensitivity analysis will be performed in the ITT population.

The proportional hazards assumption in the Cox model will be assessed. A piecewise Cox model will be considered given evidence of non-proportional hazards.

10.5 Analysis of secondary variables

Secondary endpoints will be analyzed following the testing procedure outlined in Section 10.4.

10.5.1 Safety variables

10.5.1.1 Bleeding events

All information obtained on bleeding events will be displayed by treatment group.

The number and percentage of patients with bleeding events will be tabulated by body system and preferred term with a breakdown by treatment. A patient with multiple bleeding events is only counted once towards the percentage of patients with bleeding events. Additional analysis by negative binomial may be carried out to compare bleeding event rates among treatment groups if sufficient bleeding events occur.

Bleeding events occurring during the extension period will be summarized as described in the SAP.

10.5.1.2 Adverse events

All information obtained on AEs will be displayed by treatment group and patient and will be summarized separately for the On-Treatment Analysis Set and the On-Treatment Extension Analysis Set.

The number and percentage of patients with AEs will be tabulated by body system and preferred term with a breakdown by treatment. A patient with multiple AEs within a body system is only counted once towards the total of this body system. Exposure-adjusted AE rates will also be summarized for both the On-Treatment Analysis Set and the On-Treatment Extension Analysis Set.

10.5.2 Vital signs

All vital signs data will be listed by treatment group, patient, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

10.5.3 ECG evaluations

All ECG data will be listed by treatment group, patient and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

10.5.4 Clinical laboratory evaluations

All laboratory data will be listed by treatment group, patient, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

10.5.5 Other safety evaluations

All injection site reaction data will be listed by treatment group, patient, and visit/time, and summarized by treatment group and visit/time as needed.

10.6 [redacted]

[redacted]

10.6.1 Pharmacodynamics

All pharmacodynamic endpoints will be summarized by visit and treatment group including the ratio to baseline for each treatment along with their associated confidence intervals.

10.6.2 Pharmacokinetics

Plasma total abelacimab concentration data will be listed by dose, patient, and visit/sampling time point. Descriptive summary statistics will be provided by dose and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

10.6.3 Pharmacokinetic / pharmacodynamic interactions

Graphical depictions of the relationship between plasma abelacimab concentrations and/or PK parameters and PD variables (for example: free FXI and aPTT) may be presented for the clinical study report.

The relationship between individual PK profiles or derived PK parameters and various efficacy/PD measurements or derived variables (for example: free FXI and aPTT) will be explored as appropriate. Additionally, the effect of relevant baseline characteristics (age, gender, body weight, baseline factor XI levels, baseline aPTT, etc.) on PK parameters and PD responses will be assessed as needed using a model-based approach that incorporates data from other studies with abelacimab. If available, these results may be summarized in the clinical study report; however, a separate analysis plan and final report for this analysis will be issued.

10.6.4 Immunogenicity

All immunogenicity results will be listed by treatment group, patient, and visit/time.

10.6.5 Exploratory biomarkers

[redacted]

[redacted] Sample size calculation

The primary endpoint is the composite of major or CRNM bleeding. The study is event driven.

Assuming a HR of 0.60 for each dose of abelacimab compared with rivaroxaban, at least 166 events will provide at least 80% power for each abelacimab arm vs. rivaroxaban with a 2-sided alpha of 0.05. Given an expected 15% per year event rate in the rivaroxaban arm, a 10% annual dropout rate (death, withdrawal of consent, lost-to-follow-up), approximately 1,200 patients should provide the requisite number of events over a total trial duration of 27 months. We will

follow the event rates with the possibility of extending enrollment phase to preserve the planned duration of the trial.

10.8 Ad hoc data reviews

Ad hoc data reviews of unblinded data may be conducted by a Sponsor team during the conduct of the study to support decision-making concerning the current study or the Sponsor's clinical development program in general. These reviews will be conducted by a limited Sponsor team not involved in the conduct of the study during the randomized period of the study.

11 Ethical considerations

11.1 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.

11.2 Responsibilities of the investigator and ethics committee

Before initiating a trial, the Investigator/institution must obtain approval/favorable opinion from the ethics committee (EC) for the trial protocol, written informed consent form, consent form updates, patient recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. 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 [redacted] monitors, auditors, [redacted] Quality Assurance representatives, designated agents of Anthos Therapeutics, ECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the Investigator must inform Anthos Therapeutics or a delegate working on their behalf immediately that this request has been made.

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

11.3 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. A Publication Committee, led by the TIMI Study Group, will oversee publication of primary and secondary results. Further details of the composition, roles, responsibilities, and processes of the Publication Committee will be documented in the Publication Committee Charter.

The information developed from this clinical study will be used by the Sponsor in connection with the development of abelacimab 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.

12 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 patients 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 Therapeutics and approved by the EC and health authorities, where required, it cannot be implemented.

12.1 Protocol Amendments

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

Amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the Health Authorities are subsequently notified by protocol amendment and the reviewing EC 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 patients included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 8 (Safety Monitoring) must be followed and the Study Lead informed.

13 References

References are available upon request

Berg J, Lindgren P, Nieuwlaat R, et al (2010) Factors determining utility measured with the EQ-5D in patients with atrial fibrillation. Qual. Life Res.; 3:381-390

Bolton-Maggs (2000) Factor XI deficiency and its management. Haemophilia; 6 (S1):100-9.

Büller HR, Bethune C, Bhanot S, et al (2015) Factor XI antisense oligonucleotide for prevention of venous thrombosis. N. Engl. J. Med.; 372: 232-40.

Cano SJ, Lamping DL, Bamber L, et al (2012) The Anti-Clot Treatment Scale (ACTS) in clinical trials: cross-cultural validation in venous thromboembolism patients. Health and Quality Of Life Outcomes; 10:120-130.

Cheng Q, Tucker EI, Pine MS, et al (2010) A role for factor XIIa-mediated factor XI activation in thrombus formation in vivo. Blood; 116:3981-9.

Corominas M, Gastaminza G, Lobera T (2014) Hypersensitivity reactions to biological drugs. J. Investig. Allergol. Clin. Immunol.; 24: 212-225.

Crosby JR, Marzec U, Revenko AS, et al (2013) Antithrombotic effect of antisense factor XI oligonucleotide treatment in primates. Arterioscler Thromb Vasc Biol. 33(7):1670-8.

Duga S, Salomon O (2013) Congenital factor XI deficiency: an update. Semin. Thromb. Hemost. 39:621–631

Gailani D, Renné T (2007) Intrinsic pathway of coagulation and arterial thrombosis. Arterioscler. Thromb. Vasc. Biol.; 27: 2507-13.

Hindricks G, Potpara T, Dagres N et al (2020) 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS) Eur Heart J. Aug 29;ehaa612.

Huisman MV, Rothman KJ, Paquette M, et al (2017) The Changing Landscape for Stroke Prevention in AF: Findings From the GLORIA-AF Registry Phase 2. J Am Coll Cardiol. 69(7):777-785.

Idusogie EE, Presta LG, Gazzano-Santoro H, et al (2000) Mapping of the C1q binding site on Rituxan, a chimeric antibody with a human IgG1 Fc. J. Immunol. 164: 4178-4184.

January CT, Wann LS, Alpert JS, et al (2014) 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol.;64(21):e1-76

January CT, Wann LS, Calkins H, et al (2019) 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol.;74(1):104-132.

JPAC - Joint United Kingdom Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (2014) 5th Handbook of Transfusion Medicine; January 2014; TSO; Norwich

Kaatz S, Ahmad D, Spyropoulos AC, et al (2015) Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease

in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost. 13(11):2119-26.

Koch AW, Schiering N, Melkko S, et al (2019) MAA868, a novel FXI antibody with a unique binding mode, shows durable effects on markers of anticoagulation in humans. Blood. 133(13):1507-1516.

Lip GY, Rasmussen LH, Olsson SB, et al (2009) Oral direct thrombin inhibitor AZD0837 for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: a randomized dose-guiding, safety, and tolerability study of four doses of AZD0837 vs. vitamin K antagonists. Eur Heart J; 30(23):2897-907.

Lip GY, Nieuwlaat R, Pisters R, et al (2010) Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest.;137(2):263-72.

Lip GY, Halperin JL, Petersen P, et al (2015) A Phase II, double-blind, randomized, parallel group, dose-finding study of the safety and tolerability of darexaban compared with warfarin in patients with non-valvular atrial fibrillation: the oral factor Xa inhibitor for prophylaxis of stroke in atrial fibrillation study 2 (OPAL-2). J Thromb Haemost; 13(8):1405-13.

Liu Q, Bethune C, Dessouki E, et al (2011) ISIS-FXIRx, a novel and specific antisense inhibitor of factor XI, caused significant reduction in FXI antigen and activity and increased aPTT without causing bleeding in healthy volunteers. Paper presented at the 53rd American Society of Hematology annual meeting and exposition, San Diego, California. Blood; 118: 209 – 209.

Livnat T, Tamarin I, Mor Y, et al (2009) Recombinant activated factor VII and tranexamic acid are haemostatically effective during major surgery in factor XI-deficient patients with inhibitor antibodies. Thromb. Haemost.; 102: 487–492.

Meijers JC, Tekelenburg WL, et al (2000) High Levels of Coagulation Factor XI as a Risk Factor for Venous Thrombosis N Engl J Med. 2000 Mar 9;342(10):696-701.

Mumford AD, Ackroyd S, et al (2014) Guideline for the diagnosis and management of the rare coagulation disorders: a United Kingdom Haemophilia Centre Doctors' Organization guideline on behalf of the British Committee for Standards in Haematology. Br J Haematol. 167(3):304-26.

O'Connell NM, Riddell AF, Pascoe G, et al (2008) Recombinant factor VIIa to prevent surgical bleeding in factor XI deficiency. Haemophilia. ;14(4):775-81.

Patel MR, Mahaffey KW, Garg J, et al (2011) Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 365(10):883-91.

Preis M, Hirsch J, Kotler A, Zoabi A, Stein N, et al. (2017) Factor XI deficiency is associated with lower risk for cardiovascular and venous thromboembolism events. Blood. 129(9): 1210-1215.Salomon O, Steinberg DM, Koren-Morag N, et al (2008) Reduced incidence of ischemic stroke in patients with severe factor XI deficiency. Blood; 111: 4113-7.

Rahman F, Kwan GF, and Benjamin E (2014) Global epidemiology of atrial fibrillation. Nat Rev Cardiol. 11(11):639-54.

Riddell A, Abdul-Kadir R, Pollard D, et al (2011) Monitoring low dose recombinant factor VIIa therapy in patients with severe factor XI deficiency undergoing surgery. Thromb. Haemost. 106: 521–527.

Ruff CT, Giugliano RP, Braunwald E, et al (2014) Comparison of the Efficacy and Safety of

New Oral Anticoagulants With Warfarin in Patients With Atrial Fibrillation: A Meta-Analysis of Randomised Trials. Lancet. 383(9921):955-62.

Salomon O, Steinberg DM, Zucker M, et al (2011) Patients with severe factor XI deficiency have a reduced incidence of deep-vein thrombosis. Thromb. Haemost.; 105: 269-73.

Shields RL, Namenuk AK, Hong, K, et al (2001) High resolution mapping of the binding site on human IgG_1 for FcγRI, FcγRII, FcγRIII, and FcRn and design of IgG_1 variants with improved binding to the FcgR. J. Biol. Chem. 276: 6591-6604.

Suri MFK, Yamagishi K, et al (2010) Novel Hemostatic Factor Levels and Risk of Ischemic Stroke: The Atherosclerosis Risk in Communities (ARIC) Study. Cerebrovasc Dis. 2010;29(5):497-502.

Weitz JI, Connolly SJ, Patel I, et al (2010) Randomised, parallel-group, multicentre, multinational phase 2 study comparing edoxaban, an oral factor Xa inhibitor, with warfarin for stroke prevention in patients with atrial fibrillation. Thromb Haemost; 104:633-41.

Weitz JI, Bauersachs R, Becker B, et al (2020) Effect of Osocimab in Preventing Venous Thromboembolism Among Patients Undergoing Knee Arthroplasty: The FOXTROT Randomized Clinical Trial. JAMA. 323(2):130-139.

Xarelto® (rivaroxaban) 15 mg film-coated tablets – Summary of Product Characteristics 2019. Medicine.org.uk. https://www.medicines.org.uk/emc/medicine/25592#STORAGE. Accessed 20Oct2020.

Xarelto® (rivaroxaban) 20 mg film-coated tablets – Summary of Product Characteristics 2019. Medicine.org.uk. https://www.medicines.org.uk/emc/product/2793/smpc. Accessed 20Oct2020.

Xarelto® (rivaroxaban) [Package Insert]. Janssen Pharmaceuticals, Inc. Titusville, NJ and Bayer HealthCare AG Leverkusen, Germany; revised March 2020. http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/XARELTO-pi.pdf. Accessed 20Oct2020.

14 Appendix 1 – Components of the CHA2DS2-VASc Score

Table 14-1 Components of the CHA2DS2-VASc Score (Lip et al 2010)

	Item	Points
C	Congestive heart failure (or left ventricular systolic dysfunction)	1
H	Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication)	1
A_2	Age ≥75 years	2
D	Diabetes Mellitus	1
S_2	Prior Stroke or TIA or systemic arterial thromboembolism	2
V	Vascular disease (e.g., peripheral artery disease, myocardial infarction, aortic plaque)	1
A	Age 65–74 years	1
Sc	Sex category (i.e., female sex)	1

15 Appendix 2 – Management of Bleeding

The management of suspected bleeding is at the discretion of the Investigator and will depend on the source/location of the bleeding and the severity. In all cases of bleeding, the Investigator should use clinical judgment in assessing the risk to the patient and monitor whether the bleeding is resolving or worsening.

See below for suggested guidance for patients randomized to abelacimab or rivaroxaban. Regardless of study drug assignment, in the event of severe or life-threatening bleeding such as bleeding resulting in hemodynamic compromise requiring intervention (such as endoscopy, angiography, or surgery) or an intracranial hemorrhage, the following steps should be considered:

- Withhold study drug and all antiplatelet agents / open label anticoagulants
- Institute standard of care for life-threatening bleeding (e.g., large bore i.v. or central venous access, type and crossmatch blood, admit to the intensive care unit, and provide hemodynamic and respiratory support, as needed)
- Administer packed red blood cells (or whole blood) as needed
- Consider measures specific to the patient's study treatment as described below

In cases of severe or life-threatening bleeding, the investigator is encouraged to contact the [redacted]

15.1 Abelacimab

Management of active bleeding in patients administered abelacimab should begin, if possible, with local measures (e.g., pressure or packing) at the site to control any bleeding, if possible. Minor bleeding events, such as epistaxis or superficial bleeding, can usually be managed conservatively using local measures without interruption of study drug treatment. As noted above, treatment of moderate to severe bleeding may require intravenous fluid replacement and blood transfusions. There is currently no specific reversal agent for abelacimab. Investigators are encouraged to call the [redacted] for further guidance.

Based on clinical experience managing FXI deficient individuals, treatment options for patients randomized to abelacimab include anti-fibrinolytic agents such as tranexamic acid (TXA), topical hemostatic agents such as fibrin glue, and pro-hemostatic blood components such as low dose recombinant activated factor VII (rFVIIa), prothrombin complex concentrate (PCC), fresh frozen plasma (FFP), and activated PCC [e.g., factor VIII inhibitor bypass activity (FEIBA)].

Of note, FXI concentrates are available in some countries (not marketed in the US); however, FXI concentrates are not likely to be effective in patients on abelacimab because the excess free abelacimab antibody in the circulation is expected to quickly neutralize the exogenous FXI.

Antifibrinolytic agents have been used extensively in FXI deficient patients. Since bleeding in FXI deficient patients typically occur in areas of high fibrinolytic activity such as the oral mucosa, nasal mucosa, and urinary tract, procedures such as dental extractions can be performed with oral antifibrinolytic therapy alone starting the night before and continuing for 7 days (Duga et al 2013). Tranexamic acid (TXA) is the most frequently used agent and can be given orally as a tablet or a 5% mouthwash, as well as intravenously. Fibrin glue has also been used to restore local hemostasis during dental surgery in patients with FXI deficiency (Duga et

al 2013) and is an option for patients administered abelacimab.

TXA, fibrin glue, and rFVIIa alone or in combination have been used to treat serious bleeding in FXI deficient patients undergoing major surgery and may be considered in the event of severe or life-threatening bleeding in patients administered abelacimab. Studies show that a regimen of low-dose rFVIIa at a dose of 30 µg/kg followed by administration of rFVIIa at a dose of 15–30 µg/kg every 2–4 hours for 24–48 hours in addition to TXA 1 g every 6 hours for 5 to 7 days can bypass the effect of FXI deficiency, restore coagulation parameters, and prevent serious bleeding after major surgery in FXI deficient patients (Riddell et al 2011, Livnat et al 2009).

In vitro thromboelastometry studies showed that rFVIIa is capable of bypassing the inhibition of FXIa produced by abelacimab in human blood and in plasma from cynomolgus monkeys. In blood from healthy human donors, the prolongation of clotting time induced by abelacimab was shortened upon addition of rFVIIa (see abelacimab IB). Recombinant FVIIa carries a boxed warning for thrombosis, so this therapy should only be used in cases of severe bleeding where the treating physician judges the benefit-risk to favor treatment with rFVIIa.

As a last resort, therapeutic plasmapheresis to remove abelacimab may be an option where definitive removal of abelacimab is required. Therapeutic plasmapheresis using FFP in exchange of patient's own plasma to remove free and total abelacimab and to restore FXI to desired levels in life-threatening bleeding could lead to definitive neutralization of the PD effects of abelacimab if necessary. Clinical experience with this approach, however, is currently lacking.

15.2 Rivaroxaban

Active bleeding in patients randomized to rivaroxaban should be managed according to local standard of care and guidelines (Hindricks et al 2020).

Active bleeding in patients administered rivaroxaban should begin with local measures (e.g., pressure or packing) at the site to control any bleeding, if possible. Minor bleeding events, such as epistaxis or superficial bleeding, can usually be managed conservatively without interruption of study drug treatment.

As noted above, treatment of moderate to severe bleeding may require intravenous fluid replacement and blood transfusions. If the last dose of rivaroxaban was within 2-4 hr, the use of activated charcoal may be considered to reduce further exposure. Specific treatment interventions to identify and manage the cause of bleeding (e.g., gastroscopy) should be performed promptly.

In cases of severe or life-threatening bleeding, reversal of the effects of rivaroxaban with andexanet alfa can be considered to restore physiological hemostasis. If unavailable, general hemostatic agents, such as 4-factor prothrombin complex concentrates (PCC) may be used. Activated prothrombin complex concentrates (aPCC), or rFVIIa can be considered; however, these can also increase the risk of thrombosis.

Investigators are encouraged to call the [redacted] for further guidance.

16 Appendix 3 – Assessment Schedules

Table 16-1 Assessment Schedule (Year 1)

Period	Screening	Treatment Period (Year 1)													
		Day				Month									
	-30 to -1	1	8	30	60	3	4	5	6	7	8	9	10	11	12
Visit Window (days)			±2	±3	±3	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5
Informed consent/Genetic consent[1]	x														
Inclusion/Exclusion criteria	x	x													
Demography/Medical History	x														
Physical Exam	S														
Height and Weight	x														
Vital signs	x	x		x					x						x
12-lead ECG	x														
HIV, Hepatitis B, Hepatitis C	S														
Serum Pregnancy and FSH	x														
Urine Pregnancy - WOCBP only		S		S		S			S			S			S
Hematology	x	x				x			x			x			x
Chemistry	x								x						x
Urinalysis	x														
PT/INR, aPTT	x	x		x		x			x			x			x
PK[2] and Free FXI / Total FXI[2]		x		x		x			x			x			x
Antidrug antibodies (ADA)[2]		x		x		x			x			x			x
Factor XI Coagulation Activity[3]		x		x		x			x			x			x
Exploratory biomarkers[3]		x													x
Genetic sample[1]		x													
EQ-5D-5L and ACTS PROs[3]		x							x						x
Telephone call visit only			x												
Study drug s.c. administration[4]		x		x	x	x	x	x	x	x	x	x	x	x	x
Study drug p.o. accountability[5]				x	x	x	x	x	x	x	x	x	x	x	x
Injection site inspection[4]		x		x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications	x	x													
AE assessment		x													

S = results are documented in source documents only

[1] The genetic informed consent is for an optional sub-study; the genetic sample can be collected at any time after the optional genetic informed consent is obtained
[2] Only collected from patients assigned to abelacimab
[3] May be collected in a subset of patients
[4] Patients assigned to abelacimab only; Dose can be administered at in-clinic or in-home visits by medically qualified, un-blinded study staff or designees as locally permitted. If administered in-home, assessments for concomitant medications, AEs, and other changes in health status will be conducted by sites via telephone or video call as locally permitted
[5] Patients assigned to rivaroxaban only; Accountability can be assessed at in-clinic visit or via virtual (e.g. video call) visit as appropriate and locally permitted

Table 16-2 Assessment Schedule (Year 2)

Period	Treatment Period (Year 2)[1]														
	Month														
	13	14	15	16	17	18	19	20	21	22	23	24	PSDD Visit	EoT Visit[6]	EoS 4-wk post-transition visit/call
Visit Window (days)	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5			
Physical Exam													S	S	
Vital signs						x						x	x	x	
12-lead ECG													x	x	
Urine Pregnancy - WOCBP only			S			S			S			S	S	S	
Hematology			x			x			x			x	x	x	
Chemistry						x						x			
PT/INR, aPTT			x			x			x			x	x	x	
PK[2] and Free FXI / Total FXI[2]			x			x			x			x	x	x	
Antidrug antibodies (ADA)[2]			x			x			x			x	x	x	
Factor XI Coagulation Activity[3]			x			x			x			x	x	x	
Exploratory biomarkers[3]												x		x	
EQ-5D-5L and ACTS PROs[3]						x						x			
Study drug s.c. administration[4]	x	x	x	x	x	x	x	x	x	x	x	x		x	
Study drug p.o. accountability[5]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Injection site inspection[4]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant medications	x												x	x	x
AE assessment	x												x	x	x

S = results are documented in source documents only; PSDD = permanent study drug discontinuation; EoT = end of treatment period; EoS = end of study

[1] Subsequent treatment years will follow the same assessment schedule as Year 2
[2] Only collected from patients assigned to abelacimab
[3] May be collected in a subset of patients
[4] Patients assigned to abelacimab only; Dose can be administered at in-clinic or in-home visits by medically qualified, un-blinded study staff or designees as locally permitted. If administered in-home, assessments for concomitant medications, AEs, and other changes in health status will be conducted by sites via telephone or video call as locally permitted
[5] Patients assigned to rivaroxaban only; Accountability can be assessed at in-clinic visit or via virtual (e.g. video call) visit as appropriate and locally permitted
[6] The EoT visit for the randomized treatment period will also serve as Day 1 for the optional extension period. Refer to Table 17-3 for the optional extension period assessments. If a patient elects not to enter the extension, they will have the EoS visit as described in the protocol.

Table 16-3 Optional Extension Period Assessment Schedule

[redacted]