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Statistical Analysis Plan

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Reviewers

The following reviews of the Statistical Analysis Plan (SAP) were conducted:

[redacted]

Glossary of Abbreviations

Abbreviation	Term
ACTS	Anti-Clot Treatment Scale
ADA	Anti-Drug Activity
AE	Adverse Event
AF	Atrial Fibrillation
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BLQ	Below Limit of Quantification
CI	Confidence Interval
CrCl	Creatinine clearance
CRNM	Clinically Relevant Non-Major
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
eCRF	Electronic Case Report/Record Form
EoS	End of Study
EoT	End of Treatment
FXI	Factor XI
GI	Gastrointestinal
HR	Hazard Ratio
INR	International Normalized Ratio
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intent-to-Treat
LLN	Lower Limit of Normal
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Medical Dictionary for Regulatory Activities
MedDRA	Mean Corpuscular Volume
NC	Not Calculated
NSAID	Non-Steroidal Anti-Inflammatory Drug
PCI	Potentially Clinically Important
PD	Pharmacodynamic
PK	Pharmacokinetic
p.o.	By mouth; orally
PPS	Per-Protocol Set
PRO	Patient-Reported Outcome
PT	Preferred Term
QOL	Quality of Life
RBC	Red Blood Cell
RDW	Red Cell Distribution Width
SAE	Serious AE
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
s.c.	Subcutaneous
SD	Standard Deviation
SI	International System of Units

Abbreviation	Term
SOC	System Organ Class
SSC	Study Steering Committee
TAFI	Thrombin Activable Fibrinolysis Inhibitor
TFLs	Tables, Figures and Listings
TEAE	Treatment Emergent AEs
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
WBC	White Blood Cell
WHO DD	World Health Organization Drug Dictionary

1. Source Documents

The Statistical Analysis Plan (SAP) was written based on the following documentation:

[redacted]

2. Protocol Details

2.1. Overall Study Design

This is a Phase 2b, 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 clinically relevant non-major (CRNM) bleeding events in patients with atrial fibrillation (AF) who are at moderate-to-high risk of ischemic stroke.

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

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

- Treatment group 1: abelacimab 90 mg subcutaneous (s.c.) monthly
- Treatment group 2: abelacimab 150 mg s.c. monthly
- Treatment group 3: rivaroxaban 20 mg orally (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]

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 (OLE period) if the study is discontinued early, and 4) transition period to appropriate standard of care (SoC) antithrombotic therapy per the discretion of the investigator through the End of Study (EoS) visit.

When the prespecified number of adjudicated clinical endpoint events for the final analysis have been reached, or if the study is to be stopped for any other reason, sites will be notified by the Sponsor's Clinical Study Team to schedule each patient for their EoT visit. As part of the EoT visit, the Investigator will make arrangements to transition the patient to the extension treatment period, or to end the study by transitioning the patient to a standard-of-care anticoagulation therapy following the guidelines in Section 7.1 of the protocol.

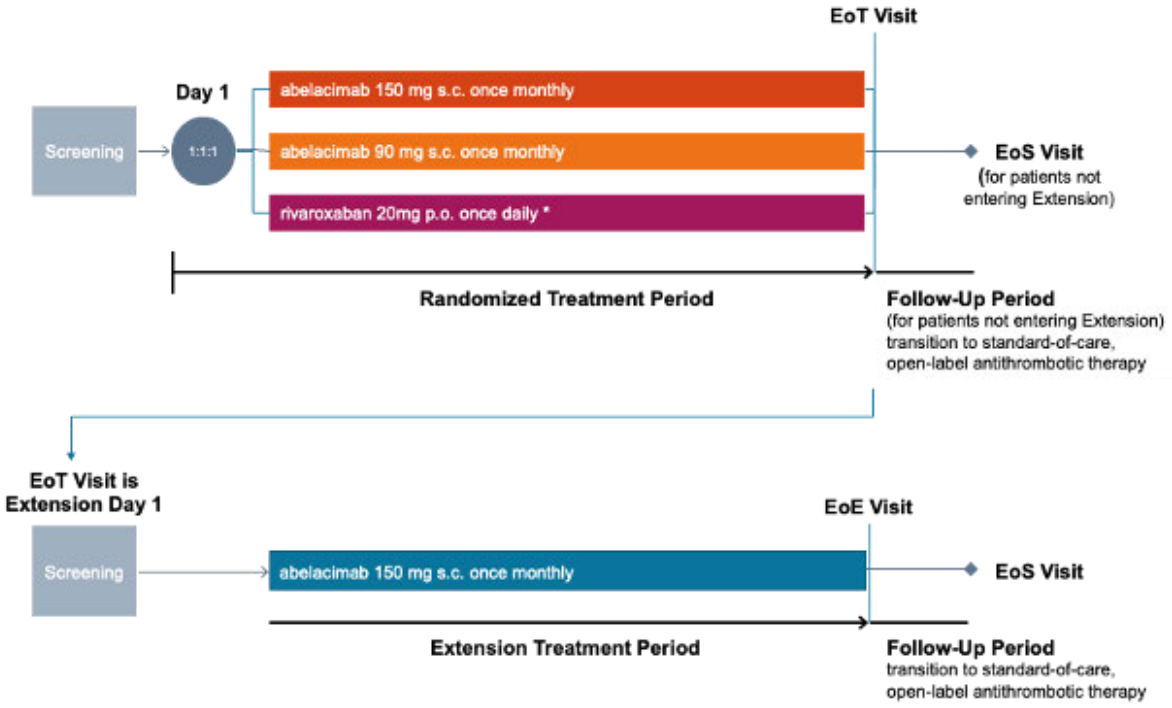
A separate statistical analysis plan will be created for the analysis of data in the study extension treatment period.

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 in the whole study. As a result, the time on study drug will vary from patient to patient, depending on when

the patient enrolls into the study in relation to when the EoT visit has occurred for each patient. Based on event rates in similar trials, the estimated duration of the study at the start of the trial was expected to be approximately 27 months, but this may take longer depending on the rate of patient recruitment and clinical endpoint event rates.

The study design is presented in Figure 1 below.

Figure 1. Overall 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

2.2. Study Objectives

2.2.1. Primary Objective

- To evaluate the effect of abelacimab relative to rivaroxaban on the rate of major or CRNM bleeding events as defined by the ISTH criteria.

2.2.2. Secondary Objectives

- To evaluate the effect of abelacimab relative to rivaroxaban on the rate of major bleeding events as defined by ISTH criteria.
- To evaluate the effect of abelacimab relative to rivaroxaban on the rate of major or minor bleeding events

2.2.3. Exploratory Objectives

- [redacted]

2.3. Sample Size and Power

The primary endpoint is the composite of major or CNRM bleeding. The study is event driven. At the start of trial it was assumed a HR of 0.60 for each dose of abelacimab compared with rivaroxaban, thereby, a total of at least 166 events would 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 would provide the requisite number of events over an approximate total trial duration of 27 months.

2.4. Primary Endpoint

- Time to first event of composite of International Society on Thrombosis and Haemostasis (ISTH)-defined major bleeding or CRNM bleeding events

2.5. Secondary Endpoints

- Time to first event ISTH-defined major bleeding events
- Time to first event ISTH-defined major or minor bleeding events

2.6. Exploratory Endpoints

- [redacted]

2.7. Safety Variables

Safety endpoints include:

- Proportion of missed doses of abelacimab compared to the proportion of missed doses of rivaroxaban
- Adverse Events (AE)
- Laboratory parameters
- Vital Signs
- Electrocardiogram (ECG)
- Injection site reactions

2.8. Pharmacokinetic/Pharmacodynamic and Other Variables

- Trough abelacimab plasma concentrations at indicated time points
- Activated partial thromboplastin time (aPTT), free factor XI (FXI), and total FXI at indicated time points
- Percentage of abelacimab-treated patients who develop anti-drug antibodies (ADAs)
- Assess the impact of ADA development to safety, efficacy, PK and PD responses
- Exploratory coagulation parameters which may include, but not limited to, [redacted]
- Exploratory evaluation of the association between [redacted]

3. Analysis Populations and Dates

3.1. Analysis Dates

The analysis dates to be used are defined as:

- EoT date = Earliest of a) the last dose+60 days or b) the EoT visit or c) death date or d) withdraw consent date or e) EoS visit date
- EoS date = Earliest of a) EoS visit or b) death date or c) withdraw consent date or d) lost to follow-up date; if no EoS date available, then impute EoT visit date

In the event that there is an open-label extension period in which the patient enrolls, the following analysis dates to be used are defined as:

- EoT date = Earliest of a) the last dose+60 days or b) the EoT visit or c) death date
- EoS date = Earliest of a) the last dose+60 days or b) the EoT visit or c) death date
- EoE date = Earliest of a) the last dose+60 days or b) the EoE visit or c) death date
- EoS extension date = EoS visit; if no EOS visit date available, then impute EoE date

In accordance with ICH E3 and E9[1], the following analysis sets will be used for the analyses.

3.2. All Screened Set

The All Screened Set will include every patient who has signed the informed consent form.

The All Screened Set will be used for summaries of disposition and the associated listings.

3.3. On-Treatment Analysis Set

On-Treatment analysis set will consist of all randomized patients who received at least one dose of study drug. Patients will be considered to be on-treatment through the EoT date as outlined in Section 3.1. On-Treatment Analysis Set patients are analyzed according to the actual treatment they received. The On-Treatment Analysis Set will be used for summaries and analysis of demographics and baseline characteristics, treatments and medications, safety endpoints, secondary endpoints, exploratory endpoints and will be the primary analysis set for the analysis of the primary endpoint.

3.4. Intent-to-Treat (ITT)

The ITT will consist of all patients randomized and dosed to be analyzed according to randomized treatment assignment. Events occurring from randomization through EoS will be included in the

analysis. The ITT analysis set will be used to perform a sensitivity analysis of the primary, secondary, and exploratory endpoints.

3.5. Per Protocol Set

The Per Protocol Set (PPS) will consist of all randomized patients with a treatment compliance rate of at least 80% and do not have any important protocol violations. The important protocol violations will be identified, documented, and finalized by the clinical study team prior to the final analysis. PPS patients are analyzed according to their randomized treatment.

Protocol deviations are defined as any change, divergence, or departure from the study design or procedures defined in the study protocol. Important protocol deviations are a subset of protocol deviations which may significantly impact the correctness, accuracy, and / or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being and are outlined in Section 3.5.1.

3.5.1. Important Protocol Deviations Leading to Exclusion from the PPS

Deviations from the protocol, as defined in the protocol deviation plan, will be documented by the study monitors and project management throughout the study period.

Only those important protocol deviations considered to have a major effect on the primary endpoint will lead to complete exclusion of the patient from the PPS. For the purposes of this study, the criteria specified in a separate document have been identified as important protocol deviations leading to exclusion from the PPS. It is considered that the occurrences of any of these criteria might have an important influence on the primary endpoint.

Criteria which require clinical or medical monitoring interpretation will be reviewed prior to database lock. All important protocol deviations leading to exclusion from the PPS occurring during the study will be reviewed and approved by Anthos prior to database lock and identified before data are unblinded.

3.6. On-Treatment Extension

The On-Treatment Extension (OTE) analysis set will consist of all patients who received at least one dose of study drug during the extension period.

3.7. Pharmacokinetics Analysis Set

The Pharmacokinetic (PK) Analysis Set will include all patients who received at least 1 dose of abelacimab and have at least 1 quantifiable PK concentration. PK Analysis Set patients are analyzed according to their actual treatment received.

3.8. Pharmacodynamics Analysis Set

The Pharmacodynamics (PD) Analysis Set will include all patients who received at least 1 dose of abelacimab and have at least 1 quantifiable PD data. PD Analysis Set patients are analyzed according to their actual treatment received.

4. Estimands

The ICH[2] E9 (R1) addendum on estimands[3] and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials came into effect on 30 July 2020. This section addresses the construction of estimands for the primary and secondary objectives.

4.1. Estimands for the primary objective

Each estimand is defined according to the following five attributes:

1) The **treatment** condition of interest, and as appropriate, the alternative condition to which comparison will be made.
2) The **population** of patients targeted by the clinical question.
3) The **variable** (or endpoint) to be obtained for each patient that is required to address the clinical question.
4) The clinical question of interest in respect of **other intercurrent events** not covered through the precise specifications of treatment, population and variable.
5) A **population-level summary** for the variable providing a basis for comparison between treatment conditions.

4.1.1. Treatment Condition of Interest

The primary treatment condition of interest is abelacimab administered s.c. once monthly and is compared against the alternative treatment condition of rivaroxaban p.o. administered once per day.

4.1.2. Population of Patients Targeted by the Clinical Question

The population targeted by the clinical question is defined through the inclusion and exclusion criteria as part of the clinical trial protocol version 5.1.

4.1.3. Variable Obtained from Each Patient Required to Address the Clinical Question

For each patient in the study, the variable to address the clinical question is time from randomization to first event of composite of ISTH-defined major bleeding or CRNM bleeding events. Patients still alive and on study without an event will be censored at the EoT date. Patients lost to follow-up or who otherwise discontinued follow-up in the study prematurely without experiencing any event will be censored at the EoT date, as defined in Section 3.1. For patients who die without experiencing a primary event before death, the time to event will be censored on the date of death.

4.1.4. Handling of Intercurrent Events to Reflect the Clinical Question of Interest

Intercurrent events will be handled through a treatment policy strategy.

The following intercurrent events are anticipated during the study:

- Death
- Treatment discontinuation
- Study discontinuation
- Concomitant anticoagulation therapy

Table 1 describes how intercurrent events will be collected and handled within the analysis.

Table 1. Handling of Intercurrent Events for the Primary Estimand

Intercurrent event	Data collection and analysis
Treatment discontinuation	Events occurring up until the EoT date will be included in the analysis. Patients without event will be censored at the EoT date.
Study discontinuation	Events occurring up until the EoT date will be included in the analysis. Patients without event will be censored at the EoT date.
Concomitant anticoagulation therapy	Patients who use concomitant anticoagulation and continue on study will be analyzed by the treatment policy strategy, i.e., no adjustment will be made. Patients who use concomitant anticoagulation without a primary event before the EoT date will be censored at the EoT date.
Death	Patients who experienced primary event before death will be included in the analysis. Patients who did not experience any bleeding event before death will be censored at the time of death reflecting a while alive strategy.

4.1.5. Population-level Summary for Comparison between Treatment Conditions

The treatment effect will be quantified by the hazard ratio comparing the hazard rate for abelacimab to the hazard rate for rivaroxaban in first occurrence of composite of ISTH-defined major bleeding or CRNM bleeding events. The basis for comparison will be 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) ≤50 ml/min.

4.2. Estimands for the secondary objectives

The estimands attributes for all secondary endpoints are defined in the same manner as for the primary endpoint described above.

5. Data Handling

5.1. Time Points and Visit Windows

5.1.1. General Definitions

All assessment days will be related to the first day of first dose of treatment.

Day 1 is defined as first dose of treatment. Relative days after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date). The day prior to Day 1 is Day -1. Day 0 is not defined.

The date of the first dose of treatment for each patient will be taken from the electronic case report/record form (eCRF) page. If the date in this eCRF page is missing, alternatively the date of randomization will be used.

The date of the last dose of treatment for each patient will be taken from the eCRF page. For subjects receiving abelacimab, the last dose is latest Date of injection from the Study Drug SC Administration eCRF page.

For subjects receiving rivaroxaban, the last dose will come from the following sources, depending on the patient status:

- For those who permanently discontinue treatment, the last dose will be the permanent discontinuation date.
- For those who died but did not permanently discontinue treatment before death, the last dose will be the death date.
- For all other subjects who completed the treatment per the EoT visit page, the last dose will be the EoT visit date.
- If the last dose date is still missing, the last dose will be the last date pills were returned from the Study Drug PO Accountability page.

5.1.2. Screening / Baseline Period

For all patients, the screening period is defined as the period from informed consent to randomization. For some variables, data from more than one assessment within the screening Period can be collected prior to randomization.

The baseline value for a variable is therefore defined as the last non-missing value collected before randomization.

Assessments carried out on day of randomization are considered to have taken place before randomization if the corresponding times have not been recorded.

5.1.3. Treatment Period

Data collected on the day of first dose will be assigned to the Treatment Period if the time (HH:MM) of data collection and time (HH:MM) of first dose of treatment are both recorded, and the data collection time is on or after the time of first dose of treatment. Otherwise, the assessment will be assigned to the screening / baseline period. If the time (HH:MM) of data collection is not recorded but the protocol and / or eCRF includes an instruction to the effect that all Day 1 assessments are to be performed prior to the first dose of treatment or randomization, the data collected at Day 1 will be assigned to the screening / baseline period, otherwise it will be assigned to the Treatment Period.

The Treatment Period is defined as the period from the date of the first dose of treatment up to and including the EoT date as defined in Section 3.1.

5.1.4. Visit Windows

All data will be analyzed using nominal study visit as defined in the Study Schedule and eCRF. No visit windows will be applied for summary and analysis unless specifically stated otherwise. For lab, data collected next month after missed scheduled visit (e.g., data collected at month 4 for missed month 3 visit) will be used for by-visit analysis.

5.2. Handling of Dropouts, Missing Data, and Outliers

5.2.1. Handling of Missing Primary Endpoint Data

Missing primary endpoint data will not be imputed.

5.2.2. Handling of Missing Safety Data

In general, missing clinical laboratory data, vital signs, and ECG data will not be imputed. Adverse event imputations for missing severity or relationship are given in Section 6.7.3. Unknown or partial medication and AE date imputations are given below and to be used only for the assessment of prior / concomitant status for medications and treatment-emergent status for AEs.

5.2.3. Handling of Partial and Missing Dates for Date of Birth, Adverse Events, Prior / Concomitant Medications

Missing or Partial Adverse Event and Prior / Concomitant Medication Start Dates

Missing and / or incomplete dates for medications and AEs are imputed in a manner resulting in the earliest onset or the longest duration during the Treatment Period, whilst ensuring that

the start date does not occur after the stop date. The stop date will not be imputed if the medication or AE is "Ongoing". Technically, this will be done as follows:

For a missing / incomplete start date / time the earliest date / time of the following will be imputed:

- The later date of: the earliest possible start date / time, and the date / time of first dose of treatment.
- The latest possible start date / time.
- The latest possible stop date / time.

For a missing / incomplete stop date / time the later date / time of the following will be imputed:

- The earlier date / time of the latest possible stop date / time and the date / time of last dose of treatment.
- The earliest possible stop date / time.
- The earliest possible start date / time.

Here, the earliest possible date / time is defined as:

- The date / time itself if available.
- The date / time of the first day of the month at 00:00hrs, if month and year are available but the day / time is missing.
- The date / time of the first day of the year at 00:00hrs, if year is available but day / time and month are missing.
- 00:00hrs on the day of informed consent, if the date / time is completely missing.

The latest possible date / time is defined as:

- The date / time itself if available.
- The date / time of the last day of the month at 23:59hrs, if month and year are available but the day / time is missing.
- The date / time of the last day of the year at 23:59hrs, if year is available but day / time and month are missing.
- 23:59hrs on the date of last known date in the study for the patient plus one day, if the date / time is completely missing.

5.2.4. Handling of Plasma Concentrations that are Below the Lower Limit of Quantification

Plasma concentrations that are below the lower limit of quantification (BLQ) will be set to half of the value between BLQ and 0 for the calculation of summary statistics.

6. Statistical Methods

6.1. General Principles

All data processing, summarization and analyses will be performed using Fortrea's SAS Environment / Version 9.4 (or later) of the SAS® statistical software package.

The default summary statistics for quantitative variables will be the number of observations (n), mean, standard deviation (SD), median, 25th and 75th percentile, minimum (min) and maximum (max), for those patients with data.

All summary statistics will be rounded (using the SAS® function ROUND) and presented to one more decimal place than the raw value, except for the minimum and maximum values that will be presented with the same decimal precision as the raw value.

For qualitative variables, the number (n) and percentage (%) of patients with non-missing data per category will be the default summary presentation, and where appropriate and present, the number of missing values as a "Missing" category. Number of patients in the analysis population will be used as denominator for percentages calculation, unless stated otherwise in Tables, Figures and Listings (TFLs) mock shell(s).

All statistical comparisons will be made using two sided tests at the α=0.05 significance level unless specifically stated otherwise. All null hypotheses will be of no treatment difference. All alternative hypotheses will be two-sided.

All laboratory test results will be received from the central laboratories, and the results will be provided in both International System of Units (SI) units and conventional units. For the TFLs, the results will be summarized or presented in SI units.

Specifications for table, figures and data listing formats can be found in the TFL shells specifications for this study.

6.2. Patient Disposition and Data Sets Analyzed

Patient disposition will be summarized by treatment group and overall, where appropriate, for the All Screened Set. The following information will be reported:

- Number of patients for the following categories:
  - Screened,
- Number and percentage of patients for the following categories:
  - Randomized,

  - Treated,
  - Not Treated,
  - Completed the study,
  - Discontinued the Study,
  - Reasons for study discontinuation.
- Number and percentage of patients included in each study population;
- Number and percentage of patients who completed / discontinued treatment, including the reasons for treatment discontinuation;
- Number and percentage of patients who met / did not meet all eligibility criteria, together with the criteria not met;
- Number and percentage of patients who failed screening prior to randomization, including the primary reason for screen failure;
- Number and percentage of patients at each site;

A patient will be regarded as having completed the study if the status recorded on the End of Study eCRF form is Complete. A patient will be considered as having discontinued the study if they have a eCRF status of premature study discontinuation.

A listing of all patients with their treatment and study completion status, including the respective reasons for treatment and study discontinuation will be presented for the ITT Set.

A listing of all screen failed patients with their reasons for screen failure including failing at least one inclusion / exclusion criteria will be presented for the All Screened Set.

6.3. Protocol Deviations

All important protocol deviations leading to exclusion from the PPS will be summarized for the On-Treatment analysis set by treatment group and overall as described below:

- The number of unique patients with at least one important protocol deviation which led to exclusion from the PPS as well as the number of patients in each important protocol deviation category will be presented by default descriptive summary statistics for categorical variables.

A listing of all patients with one or more important protocol deviations will be presented for the On-Treatment analysis set.

6.4. Demographic and Other Baseline Characteristics

6.4.1. Demographic Characteristics

Demographic characteristics will be summarized for the On-Treatment Analysis Set by treatment group and overall as described below. All missing data will be presented as part of a missing category, if appropriate. Standard descriptive statistics will be presented for the continuous variables of:

- Age (years)
- Height (cm) at screening visit
- Weight (kg) at screening visit
- Body mass index (kg/m^2) at screening visit
- Body Temperature (degrees Celsius) at screening visit
- Systolic Blood Pressure (SBP [mmHg]) at screening visit
- Diastolic Blood Pressure (DBP [mmHg]) at screening visit
- Pulse Rate (beats per minute [bpm]) at screening visit

Total counts and percentages of patients will be presented for the categorical variables of:

- Age group (years):
    - < 65
    - 65 - 74
    - ≥75
- Sex
- Race
- Ethnicity

Demographic characteristics will be listed for the On-Treatment Analysis Set.

6.4.2. Baseline Characteristics

Baseline characteristics will be summarized for the On-Treatment Analysis Set by treatment group and overall as described below. All missing data will be presented as part of a missing category, if appropriate.

Total counts and percentages of patients will be presented for the categorical variables of:

- Stratification factors: the use of concomitant antiplatelet use at baseline (yes/no) and renal function (CrCl ≤50 ml/min or CrCl >50 ml/min).
- Targeted medical background
    - Pattern of atrial fibrillation
    - Average weekly alcohol intake
    - History of heart failure
    - Most recent left ventricular ejection fraction
    - Hypertension
    - Diabetes mellitus
    - History of carotid artery disease
    - Peripheral arterial disease
    - Coronary artery disease
    - Myocardial infarction
    - History of bleeding
    - History of Gastrointestinal (GI) bleeding
    - Prior Cerebrovascular Disease
    - Prior Cerebrovascular Disease (Yes/No)
    - Associated hemorrhagic conversion
- Baseline medications
    - Currently taking any Aspirin Therapy
    - Aspirin Therapy frequency
    - Continue aspirin after randomization
    - Aspirin most frequently used
    - Currently taking any P2Y12 inhibitor
    - P2Y12 inhibitor type
    - P2Y12 inhibitor frequency
    - Continue P2Y12 inhibitor after randomization
    - Currently taking any antiplatelet therapy (other than Aspirin and P2Y12 inhibitor)
    - Currently taking an anticoagulant

- Anticoagulant
- Currently taking any oral or IV/IM NSAID (non-steroidal anti-inflammatory drug including COX-1 and COX-2 inhibitors) either prescription or non-prescription (Do not include Aspirin in this category)
- Received anticoagulation therapy for >= 60 days consecutively at any time in their life

Standard descriptive statistics will be presented for the continuous variables of targeted medical background:

- Days of most recent episode of atrial fibrillation to randomization date, which will be calculated as (randomization date - date of most recent episode of atrial fibrillation)
- Days of Prior Cerebrovascular Disease to randomization date, which will be calculated as (randomization date - date of Prior Cerebrovascular Disease)

Standard descriptive statistics will be presented for the continuous variables of baseline medications:

- Aspirin Therapy Dose (mg)
- P2Y12 inhibitor Dose (mg)

No formal tests of statistical significance will be performed on the demographic and baseline characteristics data.

Baseline characteristics will be listed for the On-Treatment Analysis Set.

6.4.3. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) [version 23.1 or a later version if updated during the study] and will be presented by System Organ Class (SOC) and Preferred Term (PT) and total. The SOCs and PTs are to be sorted by Internationally Agreed order SOCs and descending PTs in the total column.

Medical history records will be summarized for the On-Treatment Analysis Set by treatment group and overall as follows:

- The number and percentage of patients with at least one medical history record will be presented.

- The number and percentage of patients with at least one medical history record within each primary SOC and PT will be presented. The summary will be sorted using the internationally agreed order for SOC and using descending order of overall numerical counts for PT. Where terms tie, these will be sorted alphabetically.

Medical history records will be listed by-patient and within-patient by medical history start date for the On-Treatment Analysis Set.

6.4.4. Prior and Concomitant Medications

All medications will be coded using the WHO Drug Global Dictionary (WHO DD), Format B3 [Version Sep 2020 (or a later version if updated during the study)], Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior medications and concomitant medications are defined as follows:

- Prior medications are those taken with a stop date and time prior to the start of the Treatment Period.
- Concomitant medications are those with a start date and time on or after the start of the Treatment Period, or those with a start date and time before the start of the Treatment Period and either a stop date and time on or after the start of the Treatment Period, or are ongoing at the start of the study.

See Section 5.2.3 for imputation of missing or partial dates for medication.

Prior and concomitant medications will be summarized separately for the On-Treatment Analysis Set by treatment group and overall as follows:

- The number and percentage of patients with at least one prior / concomitant medication will be presented.
- The number and percentage of patients with at least one prior / concomitant medication within each therapeutic class (ATC Level 2), chemical Subgroup (ATC Level 4), and preferred term will be presented. The summary will be sorted using numerical counts by descending order of Anatomical Group, then descending order of Therapeutic Subgroup, then descending order of preferred term in the total column. Where groups or terms tie these will be sorted alphabetically.

Prior medications and concomitant medications will be listed separately for the On-Treatment Analysis Set. In the listings the relative start and stop day of prior / concomitant medication use will be calculated relative to the first dose date of treatment and will be presented for those patients who received at least one dose of treatment. If the concomitant medication is

"Ongoing" it will be indicated as such in the listing and the relative stop day will not be calculated. Only original dates will be presented in the listing even though the relative day may be based on an imputed date.

6.5. Measurements of Treatment Compliance

Treatment compliance for abelacimab is defined as the number of injections that were actually administered relative to the number of injections that should have been administrated as per the protocol for the duration of actual treatment exposure.

In general, the percentage overall compliance for abelacimab, assessed by injections count, will be calculated as follows:

$$\text{Compliance (\%)} = \frac{\text{Number of injections actually administrated}}{\text{Number of injections that should have been administrated}} \times 100\%$$

Treatment compliance for rivaroxaban is defined as the number of tablets that were actually taken relative to the number of tablets that should have been taken as per the protocol for the duration of actual treatment exposure.

In general, the percentage overall compliance for rivaroxaban, assessed by tablets count, will be calculated as follows:

$$\text{Compliance (\%)} = \frac{\text{(Total Number of tablets dispensed – Total Number of tablets returned)}}{\text{Number of tablets that should have been taken}} \times 100\%$$

The calculated percentage compliance will be categorized as:

- $< 80\%$ compliance
- $\geq 80\%$ to $\leq 125\%$ compliance
- $> 125\%$ compliance

Compliance will be summarized for the On-Treatment Analysis Set by treatment group as follows:

- Percent compliance will be presented by default summary statistics.
- Number and percentage of patients within each of the compliance categories will be presented. Any patients with missing data will be presented as part of a "Missing" category.

Treatment compliance will be listed together with exposure for the On-Treatment Analysis Set. Missing data will not be imputed and only original data for those fields (for example,

date fields) will be presented in the listing together with derived variables such as the calculated compliance (%) and exposure duration.

6.6. Primary Analysis

6.6.1. Primary Analysis

The primary endpoint variable is defined as time to first event of composite of ISTH-defined major bleeding or CRNM bleeding events occurring from randomization through EoT date. Patients alive and on-study without an event will be censored at the EoT date. Patients lost to follow-up or who otherwise discontinued study follow-up prematurely without experiencing any event will be censored at the EoT date, as defined in Section 3.1. Patients who did not experience any event before death will be censored at the earlier of the date of death and EoT date.

The primary analysis will compare each abelacimab regimen with rivaroxaban for the time from randomization to first occurrence of major or CRNM bleeding in the On-Treatment Analysis Set. For each treatment regimen, the event rates at 6-month intervals will be estimated with 95% confidence intervals (CIs). For each comparison, the time to first event will be tested using the stratified log-rank test and the treatment effect estimated 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) ≤50 ml/min

The hazard ratios with 95% CIs and two-sided p-values 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.

An inverted Kaplan-Meier plot will be drawn and estimates of the event rate at 6-month intervals will be presented.

6.6.2. Sensitivity for the Primary Analyses

The following sensitivity analyses will be performed:

1. A sensitivity analysis will be performed in the ITT Analysis Set in which events occurring from randomization through EoS date (as defined in Section 3.1) will be included. Patients without an event will be censored at the EoS date. Patients lost to follow-up or who otherwise discontinued study prematurely without experiencing any

event will be censored at their EoS date. Patients who did not experience any event before death will be censored at the earlier of the date of death and EoS date.

2. A sensitivity analysis will be performed in the PPS Analysis Set in which events occurring from randomization through end of treatment will be included similar to the On-Treatment Analysis Set.
3. A sensitivity analysis will be performed in the On-Treatment Analysis Set that will additionally censor patients once they start receiving concomitant anticoagulation therapy.
4. A sensitivity analysis will be performed in the On-Treatment Analysis Set that pools the abelacimab dose arms together and compares the pooled abelacimab groups with rivaroxaban.

If the trial is stopping following an independent Data Monitoring Committee (DMC) review, an additional sensitivity analysis will be performed using the data that was used for the DMC analysis where patients without an event will be censored on the earlier of the EoT date or the day of the data cut used for the DMC analysis.

The proportional hazards assumption in the Cox model will be assessed graphically on the Kaplan Meier plot. A piecewise Cox model will be considered if there is evidence of non-proportional hazards.

6.6.3. Secondary Analysis

6.6.3.1. Time to first ISTH-defined major bleeding event

This endpoint will be analyzed following the procedures outlined in Section 6.6.1.

6.6.3.2. Time to first ISTH-defined major or minor bleeding event

This endpoint is defined as the time to the first ISTH-defined bleeding event equal to or more severe than minor, ie, major bleeding event, CRNM bleeding event, or minor bleeding event. This will be analyzed following the procedures outlined in Section 6.6.1.

6.6.4. Exploratory Analysis

[redacted]

[redacted]

[redacted]

[redacted]

6.7. Safety

6.7.1. Extent of Exposure

Duration of exposure to abelacimab will be defined in months as:

- Exposure (months) = ([date of last dose – date of first dose] + 1) / (365.25 / 12)

The duration of exposure to rivaroxaban will be defined in months as:

- Exposure (months) = ([date of last drug returned – date of first drug dispensed] + 1) / (365.25 / 12)

Exposure durations will be calculated regardless of any interruption in dosing between the first and the last dose. If date of first dose date is missing, then date of randomization visit will be used. If last dose date is missing, the patient's EoT date will be used for analysis purpose.

The calculated exposure duration of exposure to abelacimab and to rivaroxaban will be categorized as:

- less than 3 months
- >= 3 months to < 6 months
- >= 6 months to <9 months
- >= 9 months to <12 months
- >= 12 months to <15 months
- >= 15 months to <18 months
- >= 18 months to <21 months
- >= 21 months to <24 months
- >= 24 months

Duration of exposure will be summarized in two ways for the On-Treatment Analysis Set by treatment group.

- Descriptive statistics will be presented for duration of exposure.
- Number and percentage of patients within each of the exposure categories will be presented.

The proportion of missed doses of abelacimab and the proportion of missed doses of rivaroxaban will be summarized.

6.7.2. 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 SOC and PT with a breakdown by treatment. A patient with multiple bleeding events is only counted once towards the percentage of patients with bleeding events.

Gastrointestinal bleeding events may include AEs with MedDRA terms associated with gastrointestinal hemorrhage or adjudicated as being located in the Upper GI or Lower GI, by the CEC.

The proportion of patients having received transfusions, as well as the number of blood units transfused will be summarized by treatment group and overall.

6.7.3. Adverse Events

All AEs recorded on the eCRF will be coded using the MedDRA dictionary [version 23.1 or a later version if updated during the study] and classified as treatment–emergent AEs (TEAEs) as follows:

- TEAEs are either events with start date on or after the start of the Treatment Period and up to the end of the study visit, or events with start date prior to the start of the Treatment Period whose severity worsens on or after the start of the Treatment Period.
- Treatment-Emergent Serious AEs (TESAEs) will be defined as TEAEs regarded by the investigator as Serious = “Yes”.
- The relationship between a TEAE and treatment is assessed as related, possibly related, or not related. A treatment-related TEAE will be defined as a TEAE considered by the investigator as related or possibly related to treatment or with unknown / missing relationship to treatment.

- Severe TEAEs are defined as TEAEs assessed as being "Severe" in severity and includes those events where the severity is missing.
- TEAEs leading to discontinuation of treatment are defined as TEAEs where action taken with study treatment is "Permanently Discontinued".

Adverse events will be summarized by default descriptive summary statistics for categorical variables for the On-Treatment Analysis Set by treatment group and overall as follows:

- An overview of TEAEs including the number and percentage of patients with at least one of each mentioned TEAE type:
    - Any TEAE
        - Leading to discontinuation of study treatment
        - Leading to death
        - mild
        - moderate
        - severe
    - Any study treatment related TEAE
        - Leading to discontinuation of study treatment
        - Leading to death
    - Any serious TEAE
        - Leading to discontinuation of study treatment
        - Leading to death
    - Any serious study treatment related TEAE
        - Leading to discontinuation of study treatment
        - Leading to death
- The number and percentage of patients reporting each TEAE and the count of number of events will be summarized by SOC and PT for the following types of TEAEs:
    - TEAEs Leading to Discontinuation of Study Treatment
    - TEAEs Leading to Death
    - TEAEs by Maximum Severity
    - TEAEs by Relationship to Treatment
    - TEAEs by Relationship and Maximum Severity

  - Study Treatment related TEAEs
  - Study Treatment Related TEAEs Leading to Discontinuation of Study Treatment
  - Study Treatment Related TEAEs Leading to Death
  - Serious TEAEs
  - Serious TEAEs Leading to Discontinuation of Study Treatment
  - Serious TEAEs Leading to Death
  - Study Treatment Related Serious TEAEs
  - Study Treatment Related Serious TEAEs Leading to Discontinuation of Study Treatment
  - Study Treatment Related Serious TEAEs Leading to Death
- The number and percentage of patients who died will be summarized by the primary reason of death
- The number and percentage of patients reporting each TEAE and the number of events will be summarized by PT for TEAEs of clinical endpoint

In the above summaries, patients with more than one TEAE within a particular SOC are counted only once for that SOC. Similarly, patients with more than one TEAE within a particular PT are counted only once for that PT.

For summaries by maximum severity, patients with multiple TEAEs within a particular SOC or PT will be counted under the category of their most severe TEAE within that SOC or PT. TEAEs with missing severity will be included (as Severe) in the overall count of patients with TEAEs, but will not be included in the counts of patients with TEAEs within a SOC or PT.

Summaries by SOCs and PTs will be sorted by SOCs by their Internationally Agreed Order (MedDRA) and PTs within SOC by descending order of total incidence. Where preferred terms tie PTs will be sorted alphabetically.

No formal statistical comparisons of AEs between treatment groups will be performed.

All AE data will be listed and Pre-treatment AEs and TEAEs will be presented together. Treatment-emergence status will be flagged in the listing. The listing will present the relative start and stop day of the AE calculated relative to the first dose of treatment and will be presented for those patients who received at least one dose of treatment. If the AE is "Ongoing" it will be indicated as such in the listing and the relative stop day will not be

calculated. Only original dates will be presented in the listing even though the relative day may be based on an imputed date.

In addition, the following listings will be presented:

- Listing of Deaths
- Listing of Serious TEAEs
- Listing of AEs Leading to Discontinuation of Study Treatment
- Listing of AEs of Clinical Endpoint

6.7.4. Laboratory Evaluations

Data for the following hematology, serum chemistry, and urinalysis analytes received from central laboratory are to be measured at the scheduled visits in the study flowchart.

Table 2. Laboratory Tests

Hematology **Test (SI unit)**	**Serum Chemistry** **Test (SI unit)**	**Urinalysis (dipstick)**

• Red Blood Cell (RBC) Count (10^{12}/L)
• Hemoglobin (g/L)
• Hematocrit (%)
• White Blood Cell (WBC) Count (10^9/L)
• Differential WBC (10^9/L and %)
  ○ Neutrophils
  ○ Lymphocytes
  ○ Eosinophils
  ○ Basophils
  ○ Monocytes
• Platelet count (10^9/L)
• Mean corpuscular volume (MCV)
• Mean corpuscular hemoglobin (MCH)
• Mean corpuscular hemoglobin concentration (MCHC)
• Red cell distribution width (RDW)
	• Alanine aminotransferase (ALT) (U/L)
	• Aspartate aminotransferase (AST) (U/L)
	• Total Bilirubin (mmol/L)
	  ○ Direct Bilirubin*
	  ○ Indirect Bilirubin*
	• Total Cholesterol (mmol/L)
	• Triglycerides (mmol/L)
	• Alkaline phosphatase (U/L)
	• Albumin (g/L)
	• Glucose (mmol/L)
	• Creatinine (mmol/L)
	• Creatinine Clearance (mL/m)
	• Blood Urea Nitrogen (mmol/L)
	• Calcium (mmol/L)
	• Potassium (mmol/L)
	• Sodium (mmol/L)
	• Uric acid (mmol/L)
	• Chloride
	• Bicarbonate
	
	Coagulation profile
	Activated Partial Thromboplastin Time (aPTT)
	Prothrombin Time (PT) / Prothrombin International Normalized Ratio (INR)
		• Specific Gravity
		• Proteins
		• Glucose
		• White Blood Cell Count
		• Red blood Cell Count

*if Total Bilirubin >2x upper limit of normal (ULN)

If the total bilirubin concentration is >2x the ULN, direct and indirect reacting bilirubin will be differentiated.

For the purposes of this study, creatinine clearance (CrCl) will be estimated by the Cockcroft-Gault equation as follows: CrCl (ml/min) = (140 − age) x weight (kg)/(72 x serum Creatinine (mg/dL)) x 0.85 (*if female*).

Samples for standard aPTT as well as PT/INR will be collected at the visits noted in the assessment schedule.

In accordance with the baseline value definition in Section 5.1.2, the absolute change from baseline will be derived as follows:

Absolute change (unit) = (post-baseline value – baseline value).

All laboratory data will be reported in SI units. All quantitative laboratory test values at each assessed visit will be compared with the relevant reference range in SI units and categorized as:

- Low: Below the lower limit of the reference range.
- Normal: Within the reference range (upper and lower limits included).
- High: Above the upper limit of the reference range.

For analysis purposes, values preceded by a "<" (i.e. those below the limits of quantification) will be considered as half of the value between the lower limit of quantification and 0; values preceded by a ">" sign (i.e. those below or above the limits of quantification) will be considered equal to the upper limit of quantification.

Laboratory data will be summarized by default descriptive summary statistics for continuous and categorical variables for the On-Treatment Analysis Set by treatment group and overall as follows:

- Observed values and change from baseline at each assessed visit for each standard continuous laboratory parameter;
- Number and percentage of patients with categorized (low, normal and high) values at each visit for hematology and serum chemistry;
- Number and percentage of patients with categorized (low, normal and high) values shift relative to the reference range at baseline compared to each post-baseline visit for the following laboratory evaluations: hemoglobin, hematocrit, total bilirubin,

alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and creatinine;

Listings of all clinical laboratory data including derived change from baseline will be provided for the On-Treatment Analysis Set. Within each listing, laboratory values outside the normal ranges will be flagged as either high or low. Box plots of laboratory parameters over time will be presented.

6.7.5. Vital Signs

The analyses described below will be conducted for the following vital signs assessments respectively:

- systolic blood pressure (mmHg);
- diastolic blood pressure (mmHg);
- pulse rate (beats/min [bpm]);
- body temperature (°C).

In accordance with the baseline value definition in Section 5.1.2, the absolute change from baseline will be derived as follows:

Absolute change (unit) = (post-baseline value – baseline value)

Vital sign values will be considered as potentially clinical important (PCI) if they meet criteria listed in Table 3.

Table 3. Criteria for Potentially Clinically Important Vital Signs Parameters

Vital Sign	Criteria for observed value	Flag
Pulse Rate	<44 bpm	Low (L)
	≥44 and <100 bpm	Normal
	≥100 and <120 bpm	High (H)
	≥120 bpm	Very High (VH)
Systolic Blood Pressure (SBP)	<90 mmHg	Low (L)
	≥90 and <140 mmHg	Normal
	≥140 and <170 mmHg	High (H)
	≥170 mmHg	Very High (VH)
Diastolic Blood Pressure (DBP)	<50 mmHg	Low (L)
	≥50 and <90 mmHg	Normal
	≥90 and <110 mmHg	High (H)
	≥110 mmHg	Very High (VH)

The following will be summarized by treatment group and overall for the On-Treatment Analysis Set:

- Observed values and change from baseline at each assessed visit for each standard vital sign parameter using default summary statistics for continuous variables;
- Number and percentage of patients with PCI values at each assessed visit for vital sign parameters listed in Table 2;
- Shifts tables from baseline based on the PCI Criteria categories to each post-baseline visit for vital sign parameters listed in Table 2;

A listing of all vital signs data including derived absolute change from baseline will be provided for the On-Treatment Analysis Set.

6.7.6. Electrocardiograms

The following electrocardiogram (ECG) assessments will be taken during the study:

- Heart rate (beats/min);
- Heart-rhythm (sinus, atrial fibrillation, other);

ECG parameters values will be considered PCI if they meet or exceed the upper limit values listed in Table 4.

Table 4. Criteria for Potentially Clinically Important ECG Values

ECG parameter (unit)	Criteria	
	Observed value	Change form baseline
Heart rate (beats/min)	≥ 100	Increase of ≥ 15
	≤ 40	Decrease of ≥ 15

The ECG findings will be summarized by treatment group and overall for the On-Treatment Analysis Set as follows:

- Observed values and change from baseline at each assessed visit for each ECG parameter using default summary statistics for continuous variables;
- The number and percentage of patients at each assessed visit for each ECG parameter using default summary statistics for categorical variables;
- The number and percentage of patients with post-baseline PCI values at each post-baseline visit;

A listing of all ECG data including derived change from baseline will be provided for the On-Treatment Analysis Set.

6.7.7. Physical Examination

Abnormalities identified from physical examination are recorded in the eCRF as Medical History or AEs as appropriate and will be listed and summarized as such [See Sections 6.4.3 (Medical History) and 6.7.3 (Adverse Events)].

6.7.8. Injection Site Reactions

All injection site reaction data will be listed by treatment group, patient, and visit/time for the On-Treatment Analysis Set.

6.7.9. Interim Analysis and Data Monitoring

While the independent Data Monitoring Committee will review accumulating data on a regular basis and will have access to unblinded data, no formal interim analysis will be performed for this study.

6.8. Pharmacokinetic/Pharmacodynamic Assessments

A listing of PK blood sample collection times and Plasma concentrations will be presented for detail analyte(s) from protocol separately for all patients for the Pharmacokinetics Analysis Set.

Pharmacokinetic concentrations will be summarized for the Pharmacokinetics Analysis Set for each timepoint by treatment group and overall using protocol scheduled times and appropriate summary statistics.

See Section 5.2.4 for the handling of Plasma concentrations that are BLQ.

6.8.1. Pharmacokinetic/Pharmacodynamic Analysis

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 lower limit of quantification and reported as zero.

All pharmacodynamic endpoints will be summarized by visit and treatment group.

Further details of PKPD analyses will be provided in a separate SAP.

6.9. Immunogenicity

Immunogenicity results will be summarized by treatment group and overall for each scheduled collection visit. Standard descriptive statistics will be presented for the observed values. Immunogenicity results will be listed for each patient by treatment group for each scheduled collection visit.

6.10. Exploratory Biomarkers

[redacted]

7. Changes in the Conduct of the Study or Planned Analysis

There were no changes in the conduct of the study at the time of preparing this SAP.

There were no changes in the analysis planned in the protocol of the study at the time of preparing this SAP.

8. Appendices

Appendix 1: Document History

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

9. References

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Statistical Analysis Plan Addendum

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)

Statistical Analysis Plan Addendum: [redacted]
Statistical Analysis Plan Addendum Date: 12Sep2024

Investigational Product: Abelacimab (MAA868)

Protocol Reference: ANT-006

[redacted]

Sponsor: ANTHOS THERAPEUTICS, INC.

Author:

[redacted]

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1. INTRODUCTION TO CHANGE DOCUMENTATION

Post database lock change on the statistical analysis plan is documented here.

This document was prepared following final database lock 08Mar2024, final SAP Version 2.0 dated 24Jul2023, and SAP addendum Version 1.0 dated 27Mar2024. The post database lock changes can be found in this document in sections 2.1-2.7. Version 1.0 updates are in sections 2.1-2.4; version 2.0 updates are in sections 2.5-2.7.

2. POST-SAP FINALIZATION CHANGES (POST DATABASE LOCK)

The changed texts in the SAP are shown in bold in sections below.

2.1. Change in the EoT date and EoS date in the randomized phase of the study for patients enrolled in the extension in section 3.1 of the SAP

The analysis dates to be used are defined as:

- EoT date = Earliest of a) the last dose+60 days or b) the EoT visit **-1 day** or c) death date or d) withdraw consent date or e) EoS visit date
- EoS date = Earliest of a) EoS visit or b) death date or c) withdraw consent date or d) lost to follow-up date; if no EoS date available, then impute EoT visit date **-1 day**

As per the protocol version 5.0, EoT visit and Extension Day 1 will occur on same day. In the event that there is an open-label extension period in which the patient enrolls, the following analysis dates to be used are defined as:

- EoT date = **Earlier of a) the last dose+60 days or b) the EoT visit -1 day**
- EoS date = **the EoT visit -1 day**
- EoE date = Earliest of a) the last dose+60 days or b) the EoE visit or c) death date
- EoS extension date = EoS visit; if no EOS visit date available, then impute EoE date

2.2. Change in the last dose dates in section 5.1.1 of the SAP

The date of the last dose of treatment for each patient will be taken from the eCRF page. For subjects receiving abelacimab, the last dose is latest Date of injection from the Study Drug SC Administration eCRF page **(before the extension day 1 for patients who enroll in the extension)**.

For subjects receiving rivaroxaban, the last dose will come from the following sources, depending on the patient status:

- For those who permanently discontinue treatment, the last dose will be the permanent discontinuation date.
- For those who died but did not permanently discontinue treatment before death, the last dose will be the death date.
- For all other subjects who completed the treatment per the EoT visit page, the last dose will be the EoT visit date **-1 day**.
- If the last dose date is still missing, the last dose will be the last date pills were returned from the Study Drug PO Accountability page.

For subjects receiving rivaroxaban who enroll in the extension, the last dose will be the EoT visit date -1 day.

2.3. Clarification on major bleeding type in section 6.6.1 of the SAP

The primary endpoint variable is defined as time to first event of composite of ISTH-defined major bleeding **(including non-intracranial events and the following cerebrovascular events: Hemorrhagic Stroke, Ischemic Stroke with Hemorrhagic Transformation, Other Intracranial/Intraspinal Hemorrhage)** or CRNM bleeding events occurring from randomization through EoT date.

2.4. Change in the Intent-to-Treat (ITT) in section 3.4 of the SAP

The ITT will consist of all patients randomized and ~~**dosed**~~ **it is** to be analyzed according to randomized treatment assignment.

Please note that this is also a change from section 10.1 of the protocol.

2.5. Definition of the Per Protocol Population

All randomized patients with a treatment compliance rate of at least 80% **that** do not have any major protocol violations **as defined following clinical review prior to database lock.**

2.6. Additional Exploratory Endpoints

The following exploratory endpoints are added:

- Time to first event of composite of International Society on Thrombosis and Haemostasis (ISTH)-defined major bleeding or CRNM or minor bleeding events
- Total number of International Society on Thrombosis and Haemostasis (ISTH)-defined major bleeding or CRNM or minor bleeding events
- Total number of International Society on Thrombosis and Haemostasis (ISTH)-defined major bleeding events
- Total number of International Society on Thrombosis and Haemostasis (ISTH)-defined CRNM bleeding events
- Total number of International Society on Thrombosis and Haemostasis (ISTH)-defined minor bleeding events

The time to event endpoint will be analyzed following the procedures outlined in Section 6.6.1 of the SAP. The total number of events endpoints will be analyzed following the procedures outlined in Section 6.6.4.1 of the SAP. The number and percentage of patients with at least one ISTH-defined major bleeding or CRNM or minor bleeding events will also be presented respectively.

2.7. Subgroup Analyses of Primary Endpoint

Subgroup analyses of primary endpoint will be performed for the following subgroups:

- Geography
    - North America
    - Outside North America

- Race
    - White
    - Non-white
- Age (Years)
    - < 65
    - 65-79
    - >= 80
- Sex
    - Male
    - Female
- Weight
    - <= 60 kg
    - > 60 kg
- Creatinine Clearance
    - <= 50 min/mL
    - > 50 min/mL
- Baseline antiplatelet use
    - Yes
    - No

Subgroup analyses will be analyzed following the procedures outlined in Section 6.6.1 of the SAP with the exception that the stratification factors are not included as adjusting factors. A forest plot of the hazard ratios and 95% CI from subgroup analyses will be presented. No adjustments will be made for multiple testing.