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Janssen Research & Development

Statistical Analysis Plan

A multicenter, randomized, placebo-controlled, pragmatic Phase 3 study investigating the efficacy and safety of rivaroxaban to reduce the risk of major venous and arterial thrombotic events, hospitalization and death in medically ill outpatients with acute, symptomatic COVID-19 infection

Protocol 39039039DVT3004; Phase 3

JNJ-39039039; BAY 59-7939 (rivaroxaban)

Amendment 1

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VERSION HISTORY

Table 1: SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	10SEP2020	Not Applicable	Initial release
2	23MAY2022	Yes	See amendment history

AMENDMENT HISTORY

SAP AMENDMENT 1

The original Statistical Analysis Plan (SAP) was finalized and issued on 10 September 2020, based on the Clinical Protocol 39039039DVT3004. This document is the SAP Amendment 1 that incorporates additional pre-specified supplemental analyses. Listed below are the changes in SAP Amendment 1.

Section and Topic	Description of changes in SAP Amendment 1
Section 1.1 "Tertiary/exploratory Objectives"	An additional endpoint for the composite of the primary efficacy outcome and emergency room visits has been included as a pre-specified exploratory endpoint of clinical interest. **Added:** *To evaluate whether rivaroxaban reduces the risk of a composite of all symptomatic venous thromboembolic events (VTE), major arterial thrombotic events (myocardial infarction [MI], ischemic stroke, acute limb ischemia, noncentral nervous system [non-CNS] systemic embolization), all-cause hospitalization, all-cause mortality, and emergency room (ER visits)*
Section 1.2 "Study Design"	A paragraph has been added updating the summary of the general statistical analysis, to reflect study closure due to operational reasons (with planned database lock on the 29 June 2022) and not reaching the requisite number of events for the original planned interim analysis. **Added:** ***Updated planned analysis*** *Due to the current state of the pandemic and the lower than expected blinded pooled event rate of the primary efficacy outcome, the study Executive Committee and Sponsor have recommended for the completion of enrollment on 31 March 2022 for operational reasons. The total number of primary efficacy outcomes have not reached the requisite targeted number of events (167 events, 50% of the original targeted number of events) for conducting an interim analysis.* *The study is planning to close with a planned database lock planned on the 29 June 2022. Given that there will be no interim analysis conducted, the final analysis will be based on an alpha of 0.05 (2-sided).*
Section 4 "Population (Analysis Sets) for Analysis"	An additional analysis phase is added to the table of analysis sets and analysis phases. This additional analysis phase is called *"First Dose to Up-to-Day 35"* to enable conducting a supplemental modified intention-to-treat analysis to evaluate the impact of the virtual nature of the trial. **Added (in table):** *This analysis phase includes all data from first dose date to Day 35 visit (Day 35 +6 days, Day 41)*
Section 5.3.3 Supplemental Analyses	An additional supplemental analysis has been added. **Added (third bullet point):** *Analysis of primary composite endpoint in the ITT population and from First Dose to Up-to-Day 35 analysis phase for a modified ITT analysis. For subjects who do not take study medication, the first dose date will be imputed as the randomization date + the median number of days from*

Section and Topic	Description of changes in SAP Amendment 1
	randomization date to treatment start date using the data from subjects who did take study medication.
Section 5.3.4 "Supplemental Analysis of Primary Efficacy and ER Visits"	Section 5.3.4 has been added to fully describe the analysis method of the additional exploratory endpoint of the composite of primary efficacy and ER visits.
Section 5.3.5 "Supplemental Analyses for Bayesian Borrowing"	**Section 5.3.5** has been added which rationalizes and pre-specifies a planned supplemental Bayesian analysis of the primary efficacy endpoint using information borrowed from a concurrent and similarly designed, randomized, double-blind Phase 2b trial of rivaroxaban compared to placebo in COVID-19 for disease progression sponsored by the Bill & Melinda Gates Medical Research Institute.
Section 5.6 "Tertiary/Exploratory Endpoint(s) Analysis"	The pre-specified endpoint for the composite of primary efficacy and ER visits has also added/listed in Section 5.6. **Added (first bullet point):** *Time to first occurrence of the composite of primary efficacy and ER visits defined as all symptomatic venous thromboembolic events (VTE), major arterial thrombotic events (myocardial infarction [MI], ischemic stroke, acute limb ischemia, noncentral nervous system [non-CNS] systemic embolization), all cause hospitalization, all-cause mortality, and ER visits*
Section 6.5 Appendix 5 "Bayesian Dynamic Borrowing"	**Appendix 5** has been added to fully describe the statistical methods of Bayesian Borrowing using the Robust Mixture Prior.
Typographic and grammatical corrections	• Consistency in capitalization updated: "*on-treatment*" has been updated to "*On-Treatment*" throughout. • Consistency in capitalization updated: "up-to-last contact" has been updated to "Up-to-Last-Contact" throughout. • "*Day 35 visit (Day 35+ days, ie, Day 41)"* has been updated to "*Day 35 visit (Day 35 +6 days, Day 41)"* to fix a typographical error.

1. INTRODUCTION

This statistical analysis plan (SAP) specifies definitions of analysis sets, key derived variables, and statistical methods for analysis of efficacy and safety for the Phase 3 study 39039039DVT3004 (also known as PREVENT-HD). Unless the key analysis method for efficacy and/or safety needs to be updated, an SAP amendment will not take place, regardless of a protocol amendment. Titles, mock-ups and programming instructions for all statistical outputs (tables, figures, and listings) are provided in a separate document entitled Data Presentation Specifications (DPS).

1.1. Objectives

Primary objective

- To evaluate whether rivaroxaban reduces the risk of a composite endpoint of major venous and arterial thrombotic events, all-cause hospitalization, and all-cause mortality compared to placebo in outpatients with acute, symptomatic COVID-19 infection

Secondary objectives

- To evaluate whether rivaroxaban reduces the risk of all symptomatic venous thromboembolic events (VTE), major arterial thrombotic events (myocardial infarction [MI], ischemic stroke, acute limb ischemia, noncentral nervous system [non-CNS] systemic embolization) and all-cause mortality in outpatients with acute, symptomatic COVID-19 infection
- To evaluate whether rivaroxaban reduces all cause hospitalization
- To evaluate whether rivaroxaban reduces the risk of symptomatic VTE
- To evaluate whether rivaroxaban reduces the need for emergency room (ER) visits
- To evaluate whether rivaroxaban reduces the risk of venous and arterial thrombotic events and all-cause hospitalization
- To evaluate whether rivaroxaban reduces the percentage of participants who are hospitalized or dead on Day 35
- To evaluate whether rivaroxaban reduces all-cause mortality

Tertiary/exploratory objectives

- To evaluate whether rivaroxaban reduces the risk of a composite of all symptomatic venous thromboembolic events (VTE), major arterial thrombotic events (myocardial infarction [MI], ischemic stroke, acute limb ischemia, noncentral nervous system [non-CNS] systemic embolization), all-cause hospitalization, all-cause mortality, and emergency room (ER visits)
- To evaluate whether rivaroxaban improves participant status (e.g., prevents worsening of World Health Organization [WHO] Research and Development [R&D] Blueprint: Novel Coronavirus Scale for Clinical Improvement) over time
- To evaluate if rivaroxaban reduces the individual component events of the primary efficacy endpoint

- To evaluate the ability of rivaroxaban to prevent the decline in oxygenation at rest or with ambulation
- To evaluate whether rivaroxaban can reduce the need for supplemental oxygen
- To evaluate whether rivaroxaban can prevent the occurrence of severe disease in hospital or death as defined by WHO scale scores of 5, 6, 7, or 8
- To evaluate whether rivaroxaban can prevent the occurrence of acute renal failure
- To evaluate whether rivaroxaban can prevent the occurrence of disseminated intravascular coagulation (DIC)
- To evaluate whether rivaroxaban can prevent the occurrence of acute respiratory distress syndrome (ARDS)
- To evaluate whether rivaroxaban can prevent the occurrence of COVID digit (defined as new onset and unexplained manifestation of pain, burning, swelling or discoloration of the fingers and toes and unlikely to be attributable to other causes)
- Collect medical resource utilization (MRU) data

Safety objectives

- To evaluate whether rivaroxaban is associated with an increase in critical site and fatal bleeding as defined by the International Society on Thrombosis and Hemostasis (ISTH) scale
- To evaluate whether rivaroxaban is associated with an increase in ISTH major bleeding
- To evaluate whether rivaroxaban is associated with an increase in non-major clinically relevant bleeding

Benefit-risk objectives

- To evaluate the benefit-risk profile of rivaroxaban by evaluating the risk differences for key efficacy and safety endpoints through Day 35

1.2. Study Design

This is a randomized, multicenter, placebo-controlled, pragmatic, event-driven Phase 3 study of rivaroxaban (10 mg once daily) with a target enrollment of approximately 4,000 participants with acute, symptomatic COVID-19 infection. As this is an event driven study, if the observed event rate is lower than expected, enrollment may exceed 4,000 participants up to approximately 5,000 participants without the need for a protocol amendment.

The study will enroll participants from large, integrated, health networks in the United States (US). There are no required in-person clinic visits required by the study. Central randomization will be implemented in this study. Participants meeting the eligibility criteria at an in-person or virtual outpatient visit will participate in an informed consent process and once consented will then be randomly allocated in a ratio of 1:1 to treatment with either rivaroxaban 10 mg once daily or matching placebo. Treatment assignment will be balanced within a clinical site by block randomization. The randomization will be stratified by the time from COVID-19 positive test to

randomization (1 to 5 days inclusive, 6 to 14 days inclusive). At the present time it is anticipated that the event rate or the treatment effect may be different in the 2 strata. These strata will be used as subgroup analyses to look for the comparability of the treatment effect begun early after the diagnosis or later after the diagnosis. To enable an adequate assessment in both strata, the sponsor may elect to limit enrollment in one of the strata.

All participants are to self-administer study drug (rivaroxaban or placebo) orally once daily, with or without food, at approximately the same time each day throughout the 35-day double-blind treatment period. The first dose should be taken as soon as possible after randomization and within 3 days of randomization if possible. The date and time of the study drug should be recorded as accurately as possible. A missed dose should be taken as soon as possible (up to 8 hours prior to the next scheduled dose), and the next scheduled dose should be taken at the regular time.

After the participant takes a dose of study drug on Day 35, the participant should discontinue study drug and complete the Day 35 (±6 days) virtual visit. The final follow-up will be on Day 49±7 days after randomization. Study drug may be interrupted for any hospitalization and all antithrombotic therapy will be at the discretion of the admitting physician. Upon hospital discharge, the participants may resume study drug or may permanently discontinue study drug treatment and may receive antithrombotic therapy per institutional guidelines. All participants should be followed until the last follow-up on Day 49±7 days. In the event that the participant is unavailable (e.g., hospitalized) or incapacitated (e.g., on a ventilator), information about the vital status and whereabouts of the participant and his/her status may be obtained from family and/or friends and information obtained should be documented in the electronic case report form (eCRF), electronic medical record (EMR) or other source records.

Original planned analysis

An interim analysis for futility or early superiority will be conducted when approximately 167 participants with primary efficacy outcome have been observed (about 50% of the targeted total number of events). The study may be stopped early for futility when it would be unlikely to establish superiority on the primary efficacy outcome and/or a positive benefit over risk of rivaroxaban compared with placebo if the study were to run to completion and the study will use O'Brien-Fleming boundary (Z=2.96, 2-sided alpha=0.003) to stop the study early for the early superiority. Alpha=0.049 will be used for the final analysis to control the family-wise type I error rate at an alpha of 0.05 (2-sided).

Updated planned analysis

Due to the current state of the pandemic and the lower than expected blinded pooled event rate of the primary efficacy outcome, the study Executive Committee and Sponsor have recommended for the completion of enrollment on 31 March 2022 for operational reasons. The total number of primary efficacy outcomes have not reached the requisite targeted number of events (167 events, 50% of the original targeted number of events) for conducting an interim analysis.

The study is planning to close with a planned database lock planned on the 29 June 2022. Given that there will be no interim analysis conducted, the final analysis will be based on an alpha of 0.05 (2-sided).

Double-blind intervention will be used to reduce potential bias during data collection and evaluation of clinical endpoints. Data that may potentially unblind the intervention assignment will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized.

An Independent Data Monitoring Committee (IDMC) will be established to monitor the progress of the study and ensure that the safety of participants enrolled in the study is not compromised. In addition, the IDMC will review results of the planned interim analysis and make a recommendation whether the study should continue as planned, continue with modification, or be terminated prematurely due to futility, safety, or early superiority.

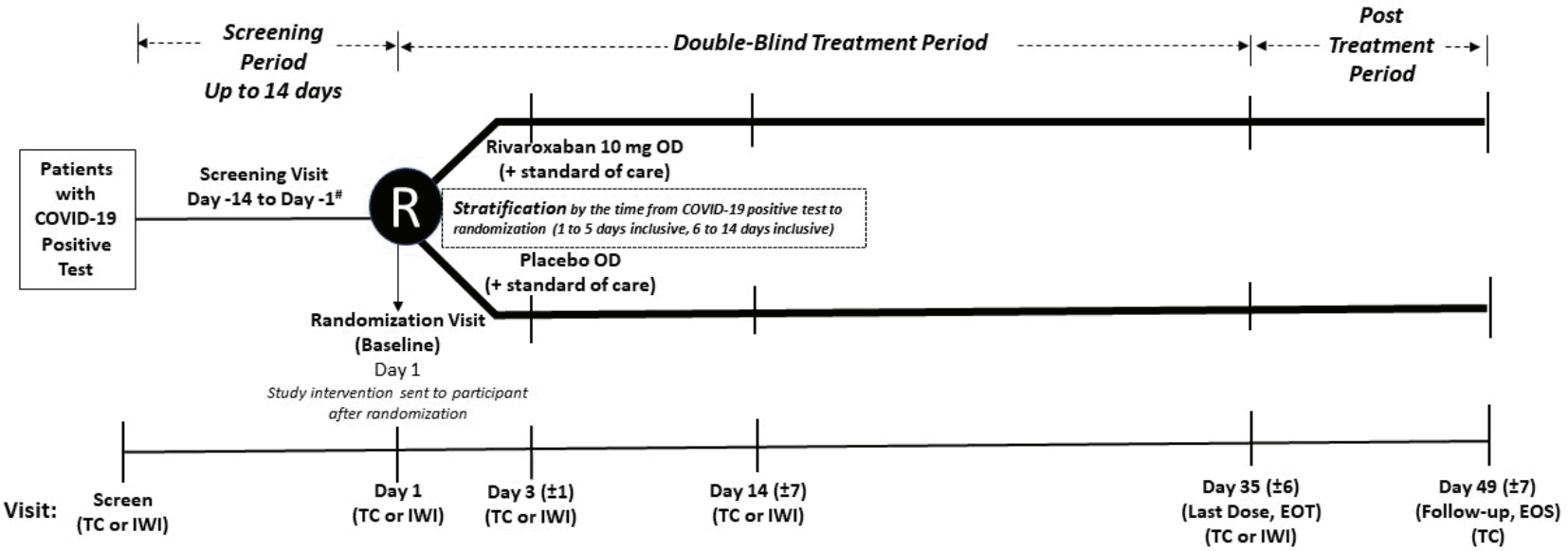
A diagram of the study design is provided below in Figure 1:

Figure 1: Schematic Overview of the Study

Key Elements:

- Patient Population: Men and women / 18 years of age or above (in the EMR system) / COVID-19 positive with symptoms / outpatient setting / at risk of thromboembolism (age ≥60, history of VTE [DVT and/or PE], CAD, PAD, CeVD/stroke, cancer, diabetes, heart failure, BMI ≥35 kg/m², elevated level of baseline D-dimer).
- Key Efficacy Outcomes*: Time to first occurrence of a composite endpoint of symptomatic VTE, MI, ischemic stroke, acute limb ischemia, systemic embolization, all-cause hospitalization, and all-cause mortality up to Day 35.
- Key Safety Outcomes*: Time to first occurrence of critical site and fatal bleeding on treatment (+2 days) (ISTH bleeding criteria).
- Key Laboratory Data*: COVID-19 diagnostic test positive and baseline level of D-dimer.

*To be collected via telephone/web contact and/or a review of eCRF/EMR, medical and pharmacy claims data, and/or Social Security Death Index.



#Screening and randomization may occur on the same day (ie, Day 1).
CAD=coronary artery disease; CeVD=cerebrovascular disease; DVT=deep vein thrombosis; eCRF=electronic case report form; EMR=Electronic medical records; EOS=end of study; EOT=end of treatment; ISTH=International Society on Thrombosis and Hemostasis; IWI=Interactive Web Interface; MI=myocardial infarction; OD=once daily; PAD=peripheral artery disease; PE=pulmonary embolism; TC=telephone contact; VTE=venous thromboembolic events

2. STATISTICAL HYPOTHESES

The primary hypothesis is to evaluate whether rivaroxaban reduces the risk of a composite endpoint of major venous and arterial thrombotic events, all-cause hospitalization and all-cause mortality compared to placebo in outpatients with acute, symptomatic COVID-19 infection during the treatment period (Day 35). The primary statistical alternative hypothesis is that rivaroxaban is superior to placebo on the primary efficacy outcome, that is, time to the first event for the rivaroxaban group is stochastically later than that for the placebo group from randomization up to Day 35. More specifically, the survival function for the placebo group is lower than that for the rivaroxaban group. The null hypothesis is that the survival function for both groups are the same.

The secondary hypotheses are that rivaroxaban is superior to placebo in the prevention of any thrombotic outcome (symptomatic VTE, MI, ischemic stroke, acute limb ischemia and non-CNS systemic embolization) and all-cause mortality, all-cause hospitalization, symptomatic VTE, ER visits, any thrombotic outcome and all-cause hospitalization, hospitalization or death on Day 35 and all-cause mortality.

3. SAMPLE SIZE DETERMINATION

This is an event-driven study. The targeted total number of primary efficacy outcome events is 333, based on the Intention-to-Treat (ITT) analysis set and Up-to-Day-35 analysis phase. If a participant has multiple events, only the first is counted towards study size determination.

This targeted total number of events is determined using statistical software PASS 15 based on the primary efficacy analysis (defined later) and the following assumptions:

- 30% relative risk reduction (RRR) in the primary efficacy outcome based on the ITT analysis set and Up-to-Day-35 analysis phase (RRR is defined as 1 minus the HR of rivaroxaban versus placebo)
- Power of 90% assuming the above RRR
- Two-sided significance level of 0.05

To observe the targeted 333 events, it is estimated that a total of approximately 4,000 participants will need to be randomized to either rivaroxaban or placebo in 1:1 ratio. This estimate is based on an estimated placebo incidence rate of the primary efficacy outcome of 10%.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Each analysis involves the following 2 aspects: 1) analysis set, specifying the subjects to be included; and 2) analysis phase, specifying the time window within which data will be included.

Analysis sets and analysis phases are defined below.

Analysis Sets	**Description**
Enrolled	All participants who sign the ICF
Randomized	The randomized analysis set includes all participants who were randomized in the study
Full Analysis Set (FAS)/Intent-To-Treat (ITT)	The full analysis set (FAS)/Intent-To-Treat (ITT) includes all randomized participants who have provided informed consent
Safety	The safety analysis set includes participants in ITT who received at least 1 dose of study intervention.
Analysis Phases	**Description**
Up-to-Day 35	This analysis phase includes all data from the randomization to Day 35 visit (Day 35 +6 days, Day 41)
On-Treatment	This analysis phase includes all data from the randomization to 2 days after the last dose of study intervention
Up-to-Last Contact	This analysis phase includes all data from the randomization to the last contact date or the death date, whichever is earlier.
First Dose to Up-to-Day 35	This analysis phase includes all data from first dose date to Day 35 visit (Day 35 +6 days, Day 41)

5. STATISTICAL ANALYSES

5.1. General Considerations

Summaries by intervention group using appropriate descriptive statistics will be provided for all study variables including demographic and baseline characteristics. No imputation will be applied, unless specified otherwise in this SAP. Descriptive statistics such as mean, median, standard deviation, minimum, and maximum will be used to summarize continuous variables. Counts and percentages will be used to summarize categorical variables. Kaplan-Meier method will be used to summarize time-to-event variables. Graphical data displays may also be used to summarize the data.

Unless stated otherwise, all statistical tests will be presented at a nominal (that is, without adjustment for multiplicity) 2-sided significance level of 0.05 and all confidence intervals (CI) at a nominal 2-sided level of 95%.

5.1.1. Visit Windows

As participants do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits to analysis visits. Listed below are the visit windows and the target days for each visit. The reference day is Study Day 1, defined as the day of randomization. If a participant has 2 or more actual visits in 1 visit window, the visit closest to the target day will be used as the protocol visit for that visit window. If 2 actual visits are equidistant from the target day within a visit window, the later visit is used.

All assignments will be made in chronological order. Once a visit date is assigned to a visit window, it will no longer be used for a later time point except for the endpoint. Listed below (Table 2) are the analysis visit windows and the target days for each visit defined in the protocol.

Table 2: Visit Windows

Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day)
1	Screening^	< 1	-14 to -1
2	Baseline/Day 1	1	1
3	Day 3	2 to 4	3
4	Day 14	7 to 21	14
5	Day 35	29 to 41	35
6	Day 49	42 to 56	49

*Relative to Study Day 1;
^ Screening may also occur on the same day as randomization (Day 1)

5.2. Participant Dispositions

Screened participants and reason for screen failures will be summarized overall.

The number of participants in the following disposition categories will be summarized throughout the study by intervention group and overall:

- Participants randomized
- Participants who received study intervention
- Participants who completed the study
- Participants who discontinued study intervention
- Reasons for discontinuation of study intervention
- Participants who terminated study prematurely
- Reasons for termination of study

The distribution of the time to discontinuation of study intervention will be displayed with Kaplan-Meier curves. Participants who terminate study intervention prematurely at any time will be considered an 'Event' and their date of study intervention discontinuation will be used in the time to event calculation. Participants who complete the study intervention will be censored and the date of last dose of study intervention will serve as the time of censoring. (Note: If the participant wishes to enroll in another investigational, randomized study while participating in the current study, then the participant should withdraw from further participation in the current study. Passive collection of EMR data and vital status may still be obtained from such participants through Day 49.)

Listings of participants will be provided for the following categories:

- Participants who discontinued study intervention prematurely
- Participants who terminated study prematurely

- Participants who were unblinded during the study period
- Participants who were randomized yet did not receive study intervention

5.3. Primary Endpoint(s) Analysis

5.3.1. Definition of Endpoint(s)

The primary efficacy endpoint is time from randomization to the first occurrence of all major venous and arterial thrombotic events (symptomatic VTE, MI, ischemic stroke, acute limb ischemia, and non-CNS systemic embolization), all-cause hospitalization, and all-cause mortality Up-to-Day-35 analysis phase.

5.3.2. Estimand

The primary estimand is described according to the following 5 attributes:

- Population: medically ill outpatients with acute, symptomatic COVID-19 infection
- Variable: time from randomization to the first occurrence of primary efficacy event Up-to-Day-35 analysis phase
- Treatments: Rivaroxaban 10 mg once daily vs placebo
- Intercurrent events (events that preclude observation of the variable or affects its interpretation): treatment discontinuation. A treatment policy strategy will be used for these intercurrent events, that is all data collected during the study irrespective of the treatment discontinuation.
- Population-level summary: HR of rivaroxaban 10 mg versus placebo, along with the 2-sided 95% Confidence Interval (CI)

This estimand targets the effect of rivaroxaban on the variable measured and follows an “ITT principle” strategy.

5.3.3. Analysis Methods

The primary statistical hypothesis will be tested using stratified log-rank test by the time from COVID-19 positive test to randomization (1 to 5 days inclusive, 6 to 14 days inclusive) with the treatment as the only variable. This primary efficacy analysis will be based on the ITT analysis set and Up-to-Day-35 analysis phase. Participants will be analyzed according to the intervention group to which they are randomized, regardless of actual treatment received. The 2-sided p-value will be reported and if it is less than the 2-sided alpha of 0.049 (adjusted for the interim analysis) at the final analysis, then superiority of the study drug will be declared.

The point estimate and corresponding 95% CI for the HR (rivaroxaban to placebo) will be provided based on the stratified Cox proportional hazards model. For the CIs, the plausibility of proportional hazards assumption will be assessed by visually comparing the plot of the log of cumulative hazard between treatments, and additionally checked by evaluating the significance of an interaction term of treatment by logarithm-transformed time in the primary Cox model. The sensitivity analysis for

the primary efficacy endpoint will be conducted using the unstratified Cox proportional hazards model. The following supplementary analyses will be performed:

- Analyses of primary composite endpoint in the safety population and the On-Treatment analysis phase.
- Analyses of primary composite endpoint in the ITT population and the Up-to-Last-Contact analysis phase.
- Analysis of primary composite endpoint in the ITT population and from First Dose to Up-to-Day 35 analysis phase for a modified ITT analysis. For subjects who do not take study medication, the first dose date will be imputed as the randomization date + the median number of days from randomization date to treatment start date using the data from subjects who did take study medication.
- Analysis of the effect size of rivaroxaban versus placebo in terms of recurrent episodes of primary efficacy outcome based on the ITT analysis set and Up-to-Day 35 analysis phase, where the total event count can be analyzed using regression methods appropriate for count data. The time at risk of recurrent primary efficacy outcome, which starts at randomization and continues until the earlier of Day 35 visit or last contact. The negative binomial regression model[1] is derived from this approach using generalized Poisson regression, with treatment as variable.
- Andersen-Gill model[2] will be explored for the time to multiple primary efficacy events. The hazard ratio for rivaroxaban versus placebo with respect to the recurrent events of primary efficacy outcome will be estimated using an unstratified Cox proportional hazards model with treatment as the only covariate, a robust estimate of the variance will be used for intra-subject correlation. The point estimate and corresponding 95% CI will be reported.

The cumulative event rate derived from Kaplan-Meier estimate will be displayed graphically to evaluate the treatment effect over time.

Homogeneity of treatment effects, both in HR and direction, in the subgroups defined in Section 5.8.3 will be explored via a test for treatment by subgroup interaction in the stratified Cox model with treatment, subgroup and the treatment-by-subgroup interaction as the covariates, stratified by the time from COVID-19 positive test to randomization (1 to 5 days inclusive, 6 to 14 days inclusive) (at a 2-sided significance level of 0.05). For time from COVID-19 positive test to randomization subgroups, unstratified Cox model will be used. Lack of a significant interaction will imply that the results are consistent across subgroups. If a significant interaction is observed, the results will be examined to determine whether the interaction is qualitative in nature using Gail-Simon test[3]. If the interaction is qualitative in nature, clinical explanations of the significant interaction will be explored. For each individual subgroup, the estimate and CI for HR will be constructed based on the Cox model except for the time from COVID-19 positive test to randomization subgroups. If the number of subjects with a primary efficacy outcome in a treatment-by-stratum cell in a subgroup is less than 5, interpretation of the CI needs to be done

5.3.4. Supplemental Analysis for Primary Efficacy and ER Visits

A supplemental analysis will be performed using a composite endpoint of primary efficacy endpoint and ER visits defined as all symptomatic venous thromboembolic events (VTE), major arterial thrombotic events (myocardial infarction [MI], ischemic stroke, acute limb ischemia, noncentral nervous system [non-CNS] systemic embolization), all-cause hospitalization, all-cause mortality, and ER visits.

The analysis will be similar to the primary estimand, using the Cox proportion hazard model, stratified by time from COVID-19 positive test to randomization (1 to 5 days inclusive, 6 to 14 days inclusive), with treatment as the only covariate. The point estimate and corresponding 95% CI for the HR (rivaroxaban to placebo) will be provided

Recurrent events will also be analyzed for the composite of the primary efficacy and ER visits, using same methods in Section 5.3.3 describing the negative binomial regression and Andersen-Gill models. Both these recurrent events analyses will use the ITT population and Up-to-Day 35 analysis phase.

5.3.5. Supplemental Analyses for Bayesian Borrowing

During the trial conduct, a literature search was conducted to identify similar externally sponsored clinical trials of anti-coagulant therapy in COVID-19. Several concurrent trials of rivaroxaban in COVID-19 treatment were identified, with results that have been formally published.

The Michelle Trial[4] is an investigator-led, open-label randomized trial in Brazil of rivaroxaban compared to no anti-coagulation for post-discharge thromboprophylaxis after hospitalization for COVID-19. Adult hospitalized with COVID-19 at increased risk of VTE (IMPROVE score ≥4 or 2-3 with D-dimer >500 ng/mL) were randomly assigned 1:1 at hospital discharge to rivaroxaban 10 mg per day or no anticoagulation for 35 days. The primary efficacy endpoint is a composite of symptomatic or fatal VTE, asymptomatic VTE on bilateral ultrasound and CT pulmonary angiogram, symptomatic arterial thromboembolism, and CV death at Day 35. The study showed in the ITT analysis, that 5/159 (3%) participants assigned to rivaroxaban and 15/159 (9%) participants assigned to no anti-coagulation arm had a primary efficacy outcome (RR = 0.33, 95% CI 0.12 – 0.90).

The ROXANE trial[5] is an investigator-led, open-label randomized trial conducted in India of rivaroxaban compared to enoxaparin for the prevention of all major, clinically relevant hemorrhagic and thrombotic events. In-patient hospitalized adults with confirmed mild or moderate COVID-19 were randomized to receive either once-daily rivaroxaban (10 mg or 15 mg) or once-daily subcutaneous enoxaparin (40 mg or 60 mg) for the intended duration of the hospital stay. The primary efficacy outcome is progression of disease requiring treatment escalation, including need for supplemental oxygen, high-flow oxygen devices or non-invasive mechanical ventilation and/or ECMO. The study showed in the ITT analysis that 4/115 (3.5%) participants assigned to rivaroxaban and 16/113 (14.2%) participants assigned to enoxaparin arm had a primary efficacy outcome of disease progression (HR = 0.207, 95% CI 0.069 – 0.621).

The Bill & Melinda Gates Medical Research Institute (Gates MRI) conducted a Phase 2b double-blind, placebo-controlled randomized trial[6] in the US to assess the safety and efficacy of rivaroxaban in people with mild COVID-19 disease who are at increased risk of disease progression, with at least one risk factor for high risk of disease progression. Participants were randomized 1:1 to either daily rivaroxaban 10 mg or placebo equivalent for 21 days, with outcomes followed-up for 35 days. Primary endpoints were safety (Grade 3/4 AE/SAEs) and progression of disease (by Gates MRI scale). Secondary endpoints included all-cause hospitalization. Reasons for all AEs were also collected and reported, including all-cause mortality and DVT. Although the trial did not show any difference in the progression of disease based on the Gates MRI scale, the ITT analysis of the secondary endpoints showed that 3/222 (1.4%) participants assigned to rivaroxaban and 7/222 (3.2%) participants assigned to placebo had all-cause hospitalization through Day 28 (RR = 0.43, 95% CI 0.10 – 1.65). Hospitalizations at any time during the study (through Day 35) in the ITT analysis occurred in 3/222 (1.4%) participants assigned to rivaroxaban and 8/222 (3.6%) assigned to placebo (RR = 0.38, 95% CI 0.10 – 1.40).

Of the published studies of rivaroxaban, there were similar degree of reductions with regards to the point estimates for similar clinical endpoints. However, the Michelle Trial and the Rivaroxaban Prophylaxis Trial were conducted in hospitalized or post-discharge populations. The Gates MRI study was conducted in the US in an outpatient population, with similarities to the PREVENT-HD inclusion criteria, with participants requiring similar VTE risk factors. Due to the similarities in trial design, including the country (US sites only), population inclusion/exclusion criteria, study medication and dosage (10 mg daily rivaroxaban), treatment duration, follow-up duration, and study endpoints collected, the Gates MRI trial results will therefore be used to construct a prior distribution for a supplemental Bayesian analysis of the primary efficacy outcome. The most similar endpoint, where possible, will be identified from the Gates MRI trial results to map to the primary efficacy outcome of the PREVENT-HD study. Where possible, additional prior distributions may be constructed for exploratory analysis of other primary, secondary, or tertiary endpoints collected by the Gates MRI trial.

By borrowing information from Gates MRI trial, a supplemental Bayesian analyses of primary efficacy outcome in the ITT population and using the Up-to-Day 35 analysis phase will be performed. A robust mixture prior[7] will be used consisting of two components: 1) informative prior based on Gates MRI trial results and a 2) vague prior to express some degree of skepticism on the borrowing strength, each with an assumed equal mixing weight of 0.5. The base-case weight of 0.5 for the prior distribution is considered a reasonable assumption, given that the PREVENT-HD trial is over double the size of the Gates MRI trial. Furthermore, the mixture also combines an equal weight of 0.5 for a vague or non-informative prior to express a degree of skepticism on the underlying borrowing strength to account for the heterogeneity between the two studies.

Mean, median, and 95% credible intervals of posterior distribution of HR will be provided and the posterior probability that HR <1. Tipping/sensitivity point analysis with mixing weights varying from 0 to 1 by intervals of 0.05 will be performed to assess the robustness of the assumption of the borrowing strength, which will identify the weight that the posterior distribution $Pr(HR < 1) \geq 97.5\%$, that is, the upper limit of 95% credible interval less than 1. For each weight, mean, median,

95% credible intervals of posterior distribution will be provided. A plot of the median with 95% credible intervals over increasing levels of borrowing strength (weight) will also be presented. Details of the analysis methods are provided Appendix 5.

5.4. Secondary Endpoint(s) Analysis

5.4.1. Key Confirmatory Secondary Endpoint(s)

5.4.1.1. Definition of Endpoint(s)

The variables for the analysis of the secondary endpoint are time from randomization to the first occurrence of the following: any thrombotic outcome (symptomatic VTE, MI, ischemic stroke, acute limb ischemia, and non-CNS systemic embolization) and all-cause mortality, all-cause hospitalization, symptomatic VTE, ER visits, any thrombotic outcome and all-cause hospitalization and all-cause mortality Up-to-Day-35 analysis phase. The other variable for the analysis of the secondary endpoint is hospitalization or death at Day 35.

5.4.1.2. Estimand(s)

The estimands for the analysis of all time to event secondary endpoints are similar as for the primary efficacy endpoint except for the attribute of variable.

The estimand for the analysis of the secondary endpoint of hospitalization or death at Day 35 is similar as for the primary efficacy endpoint except variable and population-level summary.

- Variable: hospitalization or death at Day 35 (Day 35±6)
- Population-level summary: Weighted relative risk (RR) of rivaroxaban 10 mg versus placebo, along with the 2-sided 95% CI

5.4.1.3. Analysis Methods

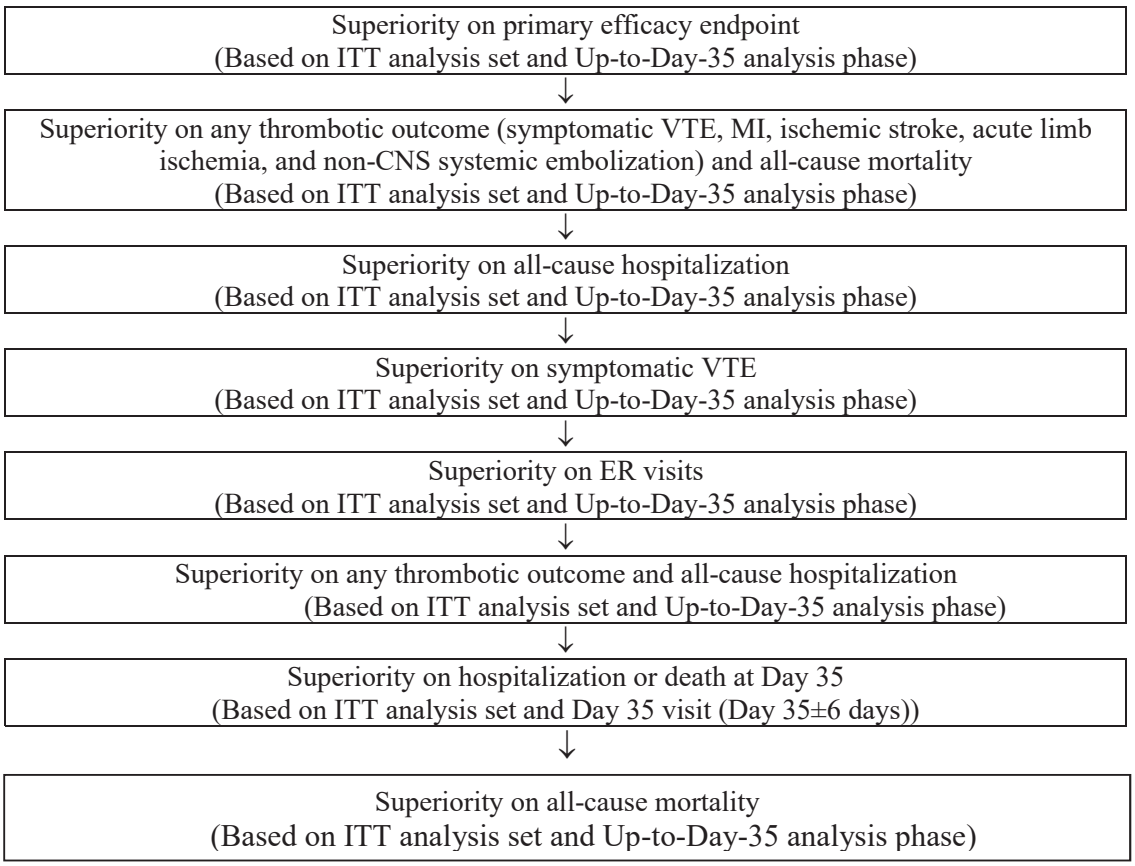
The analysis for all secondary efficacy outcomes will proceed as in the primary efficacy analysis, except for the incidence of all-cause hospitalization and all-cause mortality which will be based on Cochran-Mantel-Haenzel approach to estimate the Weighted RR and 95% CI.

Other analyses described above for the primary efficacy outcome may be performed for secondary efficacy outcomes.

5.5. Multiple Testing Procedure

To control the family-wise type I error rate at alpha of 0.05 (2-sided) in testing for efficacy outcomes, if superiority of rivaroxaban over placebo on the primary efficacy outcome is established, superiority of rivaroxaban over placebo on secondary outcomes will be tested using a hierarchical closed testing procedure in the order listed below, each at alpha of 0.05 (2-sided). If an individual test during any step is not statistically significant, subsequent tests will not be declared to be statistically significant.

The following is a diagram of the multiple testing procedure.



5.6. Tertiary/Exploratory Endpoint(s) Analysis

Tertiary/exploratory endpoints are:

- Time to first occurrence of the composite of primary efficacy and ER visits defined as all symptomatic venous thromboembolic events (VTE), major arterial thrombotic events (myocardial infarction [MI], ischemic stroke, acute limb ischemia, noncentral nervous system [non-CNS] systemic embolization), all cause hospitalization, all-cause mortality, and ER visits
- WHO R&D Blueprint: Novel Coronavirus Scale for Clinical Improvement over time
- Time to first occurrence of a component event of the primary efficacy endpoint MI, ischemic stroke, acute limb ischemia, non-CNS systemic embolization, and all-cause hospitalization) up to Day 35
- The incidence of participants achieving an O_{2sat} below 92% on room air up to Day 35
- The incidence of participants achieving an O_{2sat} below 88% on room air up to Day 35
- The incidence of participants requiring supplemental oxygen up to Day 35

- Time to first occurrence of the use of non-invasive ventilation or high-flow oxygen (WHO 5), intubation and mechanical ventilation (WHO 6), or ventilation and additional organ support (vasopressors, renal replacement therapy [RRT], extracorporeal membrane oxygenation [ECMO]; WHO 7) up to Day 35
- The incidence of participants requiring dialysis or having an estimated glomerular filtration rate (eGFR) < 15 ml/min/1.73 m^2 on two measurements more than 24 hr apart up to Day 35
- Time to first occurrence of Disseminated Intravascular Coagulation (DIC) up to Day 35
- Time to first occurrence of Acute Respiratory Distress (ARDS) up to Day 35
- The incidence of occurrence of COVID digit up to Day 35
- MRU data over time

Each tertiary/exploratory endpoint will be summarized by intervention groups based on the ITT analysis set and Up-to-Day-35 analysis phase.

5.7. Safety Analyses

All safety analyses will be based on the safety analysis set based on actual intervention received, unless otherwise specified.

For all continuous safety variables, descriptive statistics by intervention group will include the N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by intervention group using frequency counts and percentages.

5.7.1. Extent of Exposure

The number and percentage of participants who receive at least one dose of study intervention will be summarized for each intervention group.

Descriptive statistics for duration of study intervention (N, mean, SD, median, and range [minimum, maximum]) will be summarized by treatment.

Study intervention duration is defined as date of last dose of study intervention – date of first dose of study intervention + 1.

For each subject, the study intervention compliance rate is estimated as follows

Compliance rate (%) = 100 * actual study intervention duration / intended study intervention duration

More specifically, the actual study intervention duration will be calculated by minimum of [last dose date, and the first primary efficacy outcome date] - first dose date + 1 - dose interruption days up to Day 35. The intended study intervention duration will be calculated by minimum of [Day 35 date, and the first primary efficacy outcome date] - first dose date + 1.

Study intervention compliance will be summarized descriptively.

5.7.2. Bleeding Events

The principal safety outcome will be analyzed based on time from randomization to the first occurrence of fatal bleeding and critical site bleeding as defined in ISTH scale. Treatments will be compared using the same analysis models as those for the primary efficacy outcome described earlier. The analysis will be based on the safety analysis set and On-Treatment analysis phase. Participants will be analyzed according to study drug received. If a participant inadvertently receives both drugs, the participant will be analyzed as in rivaroxaban group.

The homogeneity of treatment effects on the first occurrence of the principal safety outcome across subgroups defined in Section 5.8.3 will be examined (at a 2-sided significance level of 0.05) via the test used for the primary efficacy outcome, based on the safety analysis set and On-Treatment analysis phase.

ISTH major, non-major clinically relevant, trivial bleeding, and all bleeding events will be analyzed based on time from randomization to the first occurrence. The same analysis as that for the principal safety outcome will be used. Major bleeding may also be assessed in an exploratory fashion using the Cunningham protocol (Cunningham 2011).

5.7.3. Adverse Event

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study intervention through the day of last dose plus 2 days is considered to be treatment emergent. If the event occurs on the day of the initial administration of study intervention, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study intervention based on partial onset date or resolution date. All reported adverse events will be included in the analysis. For each adverse event, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

Summary tables will be provided for adverse events:

- Post-baseline (on or after the first study drug) AEs
- Treatment-emergent adverse events
- Adverse events with onset > 2 days from the stop of study drug
- Post-baseline Serious AEs (SAEs)
- Treatment-emergent SAEs (TESAEs)
- SAEs with onset > 2 days from the stop of study drug
- AEs leading to permanent study drug discontinuation
- AEs by severity

- AEs by relationship to study intervention
- AEs with outcome of death

In addition, incidences of some of the above adverse events by system organ class and dictionary-derived (preferred) term will be provided.

In addition to the summary tables, listings will be provided for participants who:

- Had SAEs
- Had AEs leading to discontinuation of study intervention

Deaths will be displayed by actual intervention received. Frequencies for the following parameters will be included in the summary table:

- Number of participants who died
- Cause of death
- Relationship to study intervention (yes/no)

A listing of participants who died will be provided.

5.7.4. Additional Safety Assessments (if applicable)

5.7.4.1. Clinical Laboratory Tests

No routine laboratory testing will be required. However, all testing available in the EMR may be utilized to assess efficacy and safety outcome events including adverse events.

5.7.4.2. Vital Signs and Physical Examination Findings

No vital signs and physical examinations will be performed. Height and weight will be assessed and reported by the participant or obtained from medical records.

5.8. Other Analyses

5.8.1. Medical Resource Utilization and Health Economics Analyses

Medical resource utilization and health economics data collection will include the ER visits, hospitalization, and duration of hospitalization and other utilization of medical resources (e.g., urgent care visits).

Medical resource utilization and health economics data will be descriptively summarized by intervention group.

5.8.2. Benefit-Risk Analyses

This section describes several key elements for benefit-risk assessment, including 1) quantification method for benefits and risks, 2) efficacy and safety outcomes included in the evaluation, 3) analysis set and analysis phase, and 4) reporting format of the results.

These analyses are primarily intended to evaluate the key benefits and risks associated with the study treatment using a structured approach. They are complementary to other efficacy and safety analyses described elsewhere in this document. The overall benefit-risk profile of the study drug will be interpreted in consideration of the analyses described here and the totality of the data.

Quantification Methods for Measuring Benefits and Risks

As noted in previous sections, the treatment RRRs for efficacy and safety will be assessed using hazard ratios (Cox proportional hazards model). Because of differences in background event rate across different types of outcome events, a preferred metric for benefit-risk assessment is rate difference. For the current benefit-risk assessment, the treatment comparison of rivaroxaban vs. placebo will be evaluated based on the excess number of events between treatments, including events intended to be reduced (benefits) and events that may be caused (harms). The excess number of events is defined as the rate difference (i.e., the difference in event rates) times a hypothetical population size (e.g., 10,000 patients). The event rate will be calculated using the following approaches:

- Incident proportions, expressed as the percentage of patients developing the event
- Kaplan-Meier Product-Limit estimates of cumulative event rates for the duration of study (up to day 35)

In addition, number-needed-to-treat to benefit (NNT) or harm (NNH) also will be used to quantify benefits and risks of the treatment, respectively, which are calculated as the reciprocal of the differences in corresponding event rates.

Efficacy and Safety Outcomes for Benefit-Risk Evaluation

The efficacy and safety outcomes that will be included in benefit-risk evaluation are generally consistent with those specified in the efficacy and safety sections of this document.

A series of analyses will compare excess numbers of events for several pairs of key efficacy and safety endpoints:

- Primary efficacy endpoint vs. fatal bleeding and critical site bleeding
- Primary efficacy endpoint excluding fatal bleeding and hospitalization primarily due to bleeding (symptomatic VTE, MI, non-hemorrhagic stroke, acute limb ischemia, non-CNS systemic embolization, non-hemorrhagic cause hospitalization, and non-hemorrhagic death) vs. fatal bleeding and critical site bleeding
- All major venous and arterial thrombotic events (symptomatic VTE, MI, non-hemorrhagic stroke, acute limb ischemia, and systemic embolization) and non-hemorrhagic death vs. fatal bleeding and critical site bleeding
- Non-hemorrhagic death vs. fatal bleeding

To enable assessing the benefit-risk profile as a whole with mutually exclusive outcomes, we may also examine excess numbers of events and NNT or NNH for the following sets of outcomes:

- Benefits

  - Non-hemorrhagic death
  - The composite of fatal MI and fatal non-hemorrhagic stroke
  - Non-fatal non-hemorrhagic stroke
  - Non-fatal MI
  - Non-fatal acute limb ischemia
  - Non-fatal non-CNS systemic embolism
  - Non-fatal VTE
    - Non-fatal symptomatic PE
    - Symptomatic lower extremity DVT
- Harms
  - Fatal bleeding
  - Non-fatal critical site bleeding
  - Non-fatal, non-critical site bleeding requiring transfusion $\geqslant$2 units and non-fatal, non-critical site Hgb drop $\geqslant$ 2 g/dL
  - Non-fatal, non-critical site bleeding requiring transfusion $\geqslant$2 units
  - Non-fatal, non-critical site Hgb drop $\geqslant$ 2 g/dL not associated with transfusion $\geqslant$2 units

In addition, other major efficacy, safety and exploratory outcomes identified in the protocol will also be evaluated in a similar fashion to support the overall benefit-risk evaluation.

Analysis Set and Analysis Phase

The primary analysis for benefit-risk evaluation will be based on the ITT analysis set and the Up-to-Day-35 analysis phase, for both efficacy and safety outcomes. However, additional analyses using analysis sets defined by other subject analysis sets and/or analysis phases as defined in this SAP may be performed as supportive analyses (e.g., safety analysis set and On-Treatment analysis phase).

The benefit-risk analyses are not intended for hypothesis testing. Therefore, no multiplicity adjustment will be applied. When 95% CIs for point estimates of the excess number of events are provided as appropriate, nominal statistical significance at the alpha level of 0.05 (2-sided) will be declared if the confidence interval excludes zero. Additions to these benefit-risk analyses may be made following unblinding to include unexpected adverse events, new subgroups of interest, or other additions as the data warrant.

The benefit-risk assessment may also be explored for the subgroups specified in Section 5.8.3, particularly for the benefit-risk pairs specified above.

Reporting Format of the Results

To facilitate the comparison and interpretation of the results, data will be presented in one of the following formats as appropriate:

- Table format showing the between-treatment differences in benefits and risks (e.g., excess number of events and NNT or NNH)
- Kaplan-Meier plots depicting between-treatment differences in benefits and risks over time
- Forest plots for comparing key benefits and risks, as well as other key efficacy and safety outcome measures

5.8.3. Definition of Subgroups

Homogeneity of treatment effects will be assessed by subgroups and their interactions with treatment. Subgroups classified at baseline may include, but are not limited to, the following:

Subgroup	Variant	Definition
Age Group	1	• 18-<60 years • >=60 years
Age Group	2	• <60 years • 60-<75 years • >=75 years
Sex		• male • female
Race	1	• White • Others
Race	2	• White • Black • Asian • Others
eGFR	1	• missing • 15-<30 mL/min/1.73 m2 • 30-<50 mL/min/1.73 m2 • >=50 mL/min/1.73 m2
eGFR	2	• missing • 15-<30 mL/min/1.73 m2 • 30-<60 mL/min/1.73 m2 • 60-<90 mL/min/1.73 m2 • >= 90 mL/min/1.73 m2
BMI		• <25 kg/m^2 • 25-<35 kg/m^2 • >=35 kg/m^2
Baseline smoking status		• former • current • never
COVID-19 positive test		• at 1-5 days • at 6-14 days
COVID-19 respiratory symptoms		• yes • no
COVID-19 constitutional symptoms		• yes • no

Subgroup	Variant	Definition
COVID-19 neurological symptoms		• yes • no
COVID-19 gastrointestinal symptoms		• yes • no
COVID-19 musculoskeletal symptoms		• yes • no
History of diabetes requiring medication		• yes • no
History of cancer		• yes • no
History of VTE		• yes • no
History of CAD		• yes • no
History of PAD		• yes • no
History of heart failure		• yes • no
History of thrombophilia		• yes • no
History of hypertension		• yes • no
History of cerebrovascular disease or ischemic stroke		• yes • no
History of COPD		• yes • no
History of asthma		• yes • no
Baseline aspirin use		• yes • no
Baseline P2Y12 use		• yes • no
Baseline aspirin or P2Y12 use		• yes • no
Baseline D-dimer level	1	• <= 1xULN • > 1xULN • No baseline D-dimer available
Baseline D-dimer level	2	• <= 1xULN • > 1xULN -<= 2xULN • > 2xULN • No baseline D-dimer available
Baseline D-dimer level	3	• <= 2xULN • >2xULN -<6xULN • >=6xULN • No baseline D-dimer available
Number of baseline risk factors		• 1 • 2 • 3 • 4 • 5 or more

5.9. Interim Analyses

An interim analysis (IA) for futility or early superiority will be conducted when approximately 167 participants with primary efficacy outcome have been observed (about 50% of the targeted total number of events).

The IDMC will review results of the planned interim analysis and make a recommendation whether the study should be continued as planned, modified, or terminated prematurely due to futility, safety, or early superiority.

The study may be stopped early for futility when it would be unlikely to establish superiority and/or a positive benefit over risk of rivaroxaban compared with placebo, if the study were to run to completion.

Judgment for early stopping for futility should be made when any one of 2 conditions below meets:

- Estimated HR on the primary efficacy outcome is 1.0 or higher based on the interim analysis (Refer to Table 3 below for the corresponding conditional power [CP]).
- Observed incidence rate of fatal bleeding or critical site bleeding On-Treatment in rivaroxaban at IA is high enough that the overall benefit-risk profile would be unlikely to be positive when assessed at the final analysis.

Table 3: Conditional Power (CP) Based on the Assumption of the Various Underlying RRRs in the Remaining Study

	RRR in the Remaining Study	CP
Estimated HR=1 at IA 90% CI: (0.77, 1.29) 70% CI: (0.85, 1.17)	30%	33%
	20%	10%
	10%	2%
	0%	0.3%

The analysis method for the primary efficacy outcome described in Section 5.3 will be used for the interim analysis. The alpha spent in the interim analysis for the testing of the primary efficacy outcome is 0.003 (two-sided) if the analysis is conducted at exact 167 events, which is determined by the O'Brien-Fleming boundary.

The IDMC should also consider the benefit-risk assessment using clinical judgment for early stopping for efficacy.

5.9.1. Independent Data Monitoring Committee (IDMC) or Other Review Board

An IDMC will be established and will review unblinded safety data periodically to ensure the safety of study subjects. In addition, the IDMC will review results of the planned interim analysis and make a recommendation whether the study should continue as planned, continue with modification, or be terminated prematurely due to futility, safety, or early superiority.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

AE	adverse events
BMI	body mass index
CI	confidence interval(s)
COA	clinical outcome assessment (paper or electronic as appropriate for this study)
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRF	case report form(s) (paper or electronic as appropriate for this study)
CTCAE	Common Terminology Criteria for Adverse Events
DIC	disseminated intravascular coagulopathy
DMC	Data Monitoring Committee
DPS	Data Presentation Specifications
DVT	deep vein thrombosis
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
EMR	electronic medical record(s)
ER	emergency room
FOIA	Freedom of Information Act
GCP	Good Clinical Practice
HR	hazard ratio
IA	interim analysis
ICF	informed consent form
IDMC	Independent Data Monitoring Committee
ISTH	International Society on Thrombosis and Hemostasis
ITT	Intention-to-Treat
LMWH	low molecular weight heparin
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MRU	medical resource utilization
NCI	National Cancer Institute
PE	pulmonary embolism
RRR	relative risk reduction
RRT	renal replacement therapy
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
US	United States
VTE	venous thromboembolism
WHO	World Health Organization

6.2. Appendix 2 Demographics and Baseline Characteristics

The number of participants in each analysis set will be summarized and listed by intervention group and overall. In addition, the distribution of participants by site ID will be presented unless otherwise noted.

Table 4 presents a list of the demographic variables that will be summarized by intervention group and overall, for the ITT analysis set(s).

Table 4: Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m^2)	
Categorical Variables	
Age (18 -<60 years, >=60 years)	Frequency distribution with the number and percentage of participants in each category.
Age (<60 years, 60-<75 years, >=75 years)	
Sex (male, female)	
Race (White, others)	
Race (White, Black, Asian, others)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
BMI (<25 kg/m^2, 25-<35 kg/m^2, >=35 kg/m^2)	
Baseline smoking status (former, current, never)	
eGFR (missing, 15 -< 30 mL/min/1.73 m2, 30 -< 50 mL/min/1.73 m2, >=50 mL/min/1.73 m2)	
eGFR (missing, 15 -< 30 mL/min/1.73 m2, 30 -< 60 mL/min/1.73 m2, 60 -< 90 mL/min/1.73 m2, >=90 mL/min/1.73 m2)	
COVID-19 positive test (at 1-5 days, at 6-14 days)	
COVID-19 respiratory symptoms (yes, no)	
COVID-19 constitutional symptoms (yes, no)	
COVID-19 neurological symptoms (yes, no)	
COVID-19 gastrointestinal symptoms (yes, no)	
COVID-19 musculoskeletal symptoms (yes, no)	
History of diabetes requiring medication (yes, no)	
History of cancer (yes, no)	
History of VTE (yes, no)	
History of CAD (yes, no)	
History of PAD (yes, no)	
History of heart failure (yes, no)	
History of thrombophilia (yes, no)	
History of hypertension (yes, no)	
History of cerebrovascular disease or ischemic stroke (yes, no)	
History of COPD (yes, no)	
History of asthma (yes, no)	
Baseline aspirin use (yes, no)	
Baseline P2Y12 use (yes, no)	
Baseline aspirin or P2Y12 use (yes, no)	
Baseline D-dimer level (<= 1xULN, > 1xULN, No baseline D-dimer)	
Baseline D-dimer level (<= 1xULN, > 1xULN -<= 2xULN, > 2xULN, No baseline D-dimer)	
Baseline D-dimer level (<= 2xULN, > 2xULN -< 6xULN, >=6xULN, No baseline D-dimer)	
Number of baseline risk factors (1, 2, 3, 4, 5 or more)	

6.3. Appendix 3 Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact participants' rights, safety or well-being, or the integrity and/or result of the clinical study. Participants with major protocol deviations will be identified prior to database lock and the participants with major protocol deviations will be summarized by intervention group. The categories of protocol deviations may include, but are not limited to, the following:

- Did not meet the inclusion or exclusion criteria
- Received wrong treatment or incorrect dose
- Did not discontinue study drug permanently according to the protocol
- Had been taking prohibited concomitant therapies as specified in the protocol

6.4. Appendix 4 Prior and Concomitant Medications

Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study intervention. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study intervention, including those that started before and continue on after the first dose of study intervention.

Summaries of concomitant medications will be presented by Anatomical Therapeutic Chemical (ATC) term, intervention group, and study phase: (prior to the first dose of study drug, during the study drug therapy period, and after last dose of study drug [post-treatment]). The proportion of participants who receive each concomitant medication will be summarized as well as the proportion of participants who receive at least 1 concomitant medication.

Prior medications will be summarized by intervention group and ATC term.

6.5. Appendix 5 Bayesian Dynamic Borrowing

Bayesian models are informed by new data acquired during a trial (the likelihood) and by other sources of information which are incorporated into the analysis via a prior distribution. Specifically, the data gathered in this current trial will form the likelihood function in the analysis of rivaroxaban compared to placebo, while Gates MRI Trial data will partially inform the prior distribution. The Bayesian model then summarizes the information in the form of a posterior distribution on the treatment effect of rivaroxaban compared to placebo. This method relies primarily on data generated from the PREVENT-HD study but also allows for the possibility of leveraging information from a concurrent and similarly designed Gates MRI trial of rivaroxaban compared to placebo.

Reparameterization

With the proportional hazards assumption, the log-transformed estimated HR (rivaroxaban to placebo) approximates a normal distribution with variance $1/d_1 + 1/d_2$, where d_1 and d_2 are the numbers of events in two treatment groups. Let θ = log(HR) be the parameter of interest, the estimate of θ can be viewed as calculated base on two samples from normal distributions $\mathrm{N}(\mu_1, 1)$ and $\mathrm{N}(\mu_2, 1)$ with sample size d_1 and d_2 respectively, where $\mu_1 - \mu_2 = \theta$.

Robust Mixture Prior

The supplemental analyses of primary composite endpoint use a Bayesian model with robust mixture prior as below:

$$w * p_G(\theta) + (1 - w) * p_V(\theta),$$

where

- $p_G(\theta)$ denotes the informative prior of θ based on the Gates Foundation trial, which is a normal distribution. Specifically, the mean and standard deviation are the estimated log(HR) and corresponding standard error from the stratified Cox proportional hazards model will be used where possible. If stratification factor of time from COVID-19 positive test to randomization is not available in the data, then the unstratified Cox proportional hazards model will be used.
- $p_V(\theta)$ denotes the vague prior of θ. It is a normal distribution with mean 0, which indicates that there is no treatment effect of rivaroxaban compared to placebo. The standard deviation is set to be the standard error of estimated θ with "one subject" per group. Therefore, two trial subjects will follow $\mathrm{N}(\mu_1, 1)$ and $\mathrm{N}(\mu_2, 1)$, respectively, with the standard deviation of 1+1=2.
- w denotes the mixing weight, and interpreted as the prior probability that the source information from Gates MRI trial is relevant for this study.

The robust mixture prior model assumes the treatment effect in the target population is similar to the reference population, but also expressing some degree of skepticism towards borrowing strength. By selecting $w = 0.5$, a moderately informative prior is chosen as the base-case.

Tipping point analysis with w varying from 0 to 1, with intervals of 0.05, will be performed to assess the sensitivity of this method.

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