Janssen Research & Development *

Clinical Protocol

Protocol Title

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

PREVENT-HD

Protocol 39039039DVT3004; Phase 3

JNJ-39039039; BAY 59-7939 (rivaroxaban)

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This compound is approved for marketing in 7 indications.

United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

Status: Approved
Date: 04 June 2020
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-RIM-60017, 1.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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1.1. Synopsis

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

Rivaroxaban is an oral, direct acting, Factor Xa (FXa) inhibitor anticoagulant that inhibits thrombus generation and thrombus formation. Rivaroxaban has been under development for the treatment of multiple thrombosis-mediated conditions. Rivaroxaban is marketed under the trade name XARELTO® and is approved for multiple indications worldwide. The clinical development program for rivaroxaban is extensive. Almost 200,000 participants have been studied from Phase 1 through multiple large Phase 4 studies as of 15 September 2019, covering several indications and potential indications in the overall clinical development program, including 115,000 participants who received rivaroxaban. For the most comprehensive nonclinical and clinical information regarding rivaroxaban, refer to the latest version of the Investigator's Brochure (IB) for rivaroxaban.

OBJECTIVES AND ENDPOINTS

Objectives	**Endpoints[a]**
Primary (Intention-to-Treat [ITT] Population)	
The primary objective will be 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 with placebo in outpatients with acute, symptomatic COVID-19 infection	The primary efficacy outcome variable will be the time to first occurrence of a composite endpoint of symptomatic venous thromboembolism (VTE), myocardial infarction (MI), ischemic stroke, acute limb ischemia, noncentral nervous system (non-CNS) systemic embolization, all-cause hospitalization, and all-cause mortality up to Day 35
Secondary (ITT Population)	
To evaluate whether rivaroxaban reduces the risk of all symptomatic VTE, major arterial thrombotic events (MI, ischemic stroke, acute limb ischemia, non-CNS systemic embolization) and all-cause mortality in outpatients with acute, symptomatic COVID-19 infection	Time to first occurrence of a composite endpoint of symptomatic VTE, MI, ischemic stroke, acute limb ischemia, non-CNS systemic embolization, and all-cause mortality up to Day 35
To evaluate whether rivaroxaban reduces all-cause hospitalization	Time to first occurrence of all-cause hospitalization up to Day 35
To evaluate whether rivaroxaban reduces the risk of symptomatic VTE	Time to first occurrence of symptomatic VTE up to Day 35
To evaluate whether rivaroxaban reduces the need for emergency room (ER) visits	Time to first occurrence of an ER visit up to Day 35

Objectives	Endpoints[a]
To evaluate whether rivaroxaban reduces the risk of venous and arterial thrombotic events and all-cause hospitalization	Time to first occurrence of symptomatic VTE, MI, ischemic stroke, acute limb ischemia, non-CNS systemic embolization, and all-cause hospitalization up to Day 35
To evaluate whether rivaroxaban reduces the percentage of participants who are hospitalized or dead on Day 35	Incidence of participants who are hospitalized or dead from any cause on Day 35
To evaluate whether rivaroxaban reduces all-cause mortality up to Day 35	Time to all-cause mortality up to Day 35
Safety Endpoints (Safety Population)	
To evaluate whether rivaroxaban is associated with an increase in critical site and fatal bleeding	Time to first occurrence of International Society on Thrombosis and Hemostasis (ISTH) critical site and fatal bleeding on treatment (+2 days)
To evaluate whether rivaroxaban is associated with an increase in major bleeding	Time to first occurrence of ISTH major bleeding on treatment (+2 days)
To evaluate whether rivaroxaban is associated with an increase in nonmajor clinically relevant bleeding	Time to first occurrence of nonmajor clinically relevant bleeding on treatment (+2 days)
Tertiary/Exploratory (ITT Population)	
To evaluate whether rivaroxaban improves participant status (eg, prevents worsening of World Health Organization [WHO] Research and Development [R&D] Blueprint: Novel Coronavirus Scale for Clinical Improvement) over time	WHO R&D Blueprint: Novel Coronavirus Scale for Clinical Improvement over time
To evaluate if rivaroxaban reduces individual component events of the primary efficacy endpoint	Time to first occurrence of a component event of the primary efficacy endpoint (MI, ischemic stroke, acute limb ischemia, and non-CNS systemic embolization) up to Day 35
To evaluate the ability of rivaroxaban to prevent the decline in oxygenation at rest or with ambulation	• The incidence of participants achieving an oxygen saturation (O_{2sat}) below 92% on room air at rest or with ambulation up to Day 35 • The incidence of participants achieving an O_{2sat} below 88% on room air at rest or with ambulation up to Day 35
To evaluate whether rivaroxaban can reduce the need for supplemental oxygen	The incidence of participants requiring supplemental oxygen up to Day 35

Objectives	Endpoints[a]
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	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) or all-cause mortality (WHO 8) up to Day 35
To evaluate whether rivaroxaban can prevent the occurrence of acute renal failure	The incidence of participants requiring dialysis or having an estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2 on 2 measurements more than 24 hours apart up to Day 35
To evaluate whether rivaroxaban can prevent the occurrence of disseminated intravascular coagulation (DIC)	Time to first occurrence of DIC up to Day 35
To evaluate whether rivaroxaban can prevent the occurrence of acute respiratory distress syndrome (ARDS)	Time to first occurrence of ARDS up to Day 35
To evaluate whether rivaroxaban can prevent the occurrence of COVID digit	The incidence of occurrence of COVID digit up to Day 35
Collect medical resource utilization (MRU) data	MRU data over time
Benefit-Risk	
To evaluate the benefit-risk profile of rivaroxaban by evaluating the risk differences for key efficacy and safety endpoints through Day 35	Evaluate the risk differences for the composite and components of the primary efficacy outcome compared with fatal and critical site bleeding through Day 35

a Study endpoints will be assessed and reported by a qualified investigator according to protocol-specified definitions.

Overall safety will be assessed.

Hypotheses

The primary hypothesis of this study is that rivaroxaban is superior to placebo in the prevention of major venous and arterial thrombotic events, hospitalization, and death in outpatients with acute, symptomatic COVID-19 infection during the treatment period (Day 35). 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 at Day 35, and all-cause mortality.

OVERALL 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, with 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 involving a centralized study staff, as well as decentralized nonstudy physicians or nonstudy healthcare providers. There are no required in-person clinic visits required by the study. Participants who complete a COVID-19 test for infection (eg, polymerase chain reaction [PCR] test) as part of standard of care within the health network and who test positive will be identified by the centralized study staff as potential study participants through review of existing electronic medical records (EMR). Potential study participants may also be recruited by nonstudy physicians in collaboration with the study sites. Participants meeting the eligibility criteria at an in-person or virtual outpatient contact 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 or placebo. At the time of screening, recently taken medications and the need for immediate anticoagulation will be considered to determine if any symptoms reported by study participants are related to a study endpoint at the time of the screening.

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. In addition, the sponsor will monitor baseline risk factors and may elect to cap enrollment of participants with a certain risk factor to enable an adequate assessment of subgroups with particular risk factors. If a decision is made to institute capping, the site will receive a written communication with instructions for implementation and a request for confirmation of receipt without the need for a protocol amendment.

Study intervention will be shipped or delivered by courier from the drug depot and/or central pharmacy to the participant's address and will be self-administered by the study participant. The study personnel will confirm receipt and initiation of study intervention by remote contact (eg, phone or email), reinforce the study purpose, review dosing instructions, and provide the participant with contact information in the event questions should arise. During the study, the study personnel will contact the participant in accordance with the Schedule of Activities (SoA) to collect specified information, including safety and efficacy outcome events, assess and document the events in the EMR or electronic case report form (eCRF). Study personnel will systematically question participants about any new or worsening symptoms suggestive of a study efficacy or safety endpoint. While assessing the nature and severity of symptoms reported by study participants, careful consideration will be given to symptoms that could be related to manifestations of either COVID-19 or venous and arterial thrombotic events (such as shortness of breath or chest pain) or overt bleeding events and will be encouraged to seek appropriate evaluation by their local health care providers.

At the completion of study intervention treatment (Day 35), the study personnel will contact the participant to confirm vital status and ask about any signs/symptoms or diagnosis of venous and arterial thrombotic events, hospitalization and its duration, bleeding events, serious adverse event collection, and will document the participant's feedback in the EMR or eCRF. The final follow-up will be on Day 49±7 days after randomization. Study intervention 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 intervention or may permanently discontinue study intervention and may receive antithrombotic therapy per institutional guidelines. Study participants may temporarily interrupt study intervention required for procedures or during evaluation for study endpoints and may be resumed if deemed appropriate by the local physician. All participants should be followed until the last follow-up on Day 49±7 days. In the event that the participant is unavailable (eg, hospitalized) or incapacitated (eg, 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, EMR or other source records, and documented in the eCRF.

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study.

NUMBER OF PARTICIPANTS

The target enrollment is 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, with up to approximately 5,000 participants, without the need for a protocol amendment.

INTERVENTION GROUPS AND DURATION

Participants will be randomly allocated in a ratio of 1:1 to treatment with either rivaroxaban 10 mg once daily or matching placebo.

All participants are to self-administer study intervention (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 2 days of randomization if possible. The date and time of the study intervention 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 intervention on Day 35, the participant should discontinue study intervention and complete the Day 35 (±6 days) virtual outpatient contact. A final follow-up visit will occur on Day 49±7 days by virtual outpatient contact as well (refer to the SoA).

All participants will be allowed to be treated with standard of care medications for COVID-19 at the discretion of the participants' local physician. If a medication must be given to a participant in the study that has an unacceptable drug interaction, the study intervention should be discontinued for as long as the negatively interacting drug must be given. Study intervention may be restarted at the discretion of the investigator if the drug with the negative interaction is discontinued. In the event that the participant wishes to participate in another study that is testing an experimental therapy, the participant should withdraw from this study. However, passive collection of EMR data and vital status may still be obtained through Day 49.

EFFICACY EVALUATIONS

Efficacy outcomes will be assessed and documented per the SoA and will include all information necessary for the following key efficacy outcomes to be assessed via telephone/web contact, from review of the eCRF, EMR, claims databases, Social Security Death Index, or other source documents: all-cause mortality (and cause of death, if known), all-cause hospitalization, MI, stroke (ischemic, hemorrhagic, unknown etiology), acute limb ischemia, non-CNS systemic embolization, symptomatic VTE (ie, symptomatic deep vein thrombosis [DVT], and pulmonary embolism [PE]).

Any event that includes symptoms or signs suggestive of symptomatic VTE events, MI, ischemic stroke, acute limb ischemia, or non-CNS systemic embolization will be assessed and entered into the eCRF as a potential event by the investigator/study team. In identifying potential events, investigators are encouraged to give careful consideration to symptoms that may represent manifestations of major venous and arterial thrombotic events and encourage participants to seek medical care. Review of EMR data for health system encounters suggestive of study events (eg, hospitalizations) may also be conducted to identify study endpoints. Source documents may be requested from nonstudy physicians within the health network or from health care encounters outside of the investigator's health network to assist in identifying all efficacy and safety outcome events.

There will be no independent adjudication by a Clinical Events Committee. Potential events will be adjudicated locally by a qualified site investigator who will review source documents, such as the EMR, eCRF, and other study records or source documents in a blinded and impartial manner to verify/adjudicate events according to the endpoint definitions. The qualified investigator will evaluate all available information from the eCRF, EMR or other source documents and will document in the eCRF whether the subject did or did not have any of the following events according to the protocol-specified definitions of the events:

- Symptomatic VTE
- Myocardial infarction
- Stroke (ischemic, hemorrhagic or unknown etiology)
- Acute limb ischemia
- Non-CNS systemic embolization

Any clinical event that suggests the possibility that an efficacy outcome event has occurred (including acute coronary syndrome and transient ischemic attack) should be recorded in the eCRFs and will be assessed by the investigator. COVID-19 has been associated with arterial emboli in a variety of locations, including internal organs (eg, mesenteric artery, renal artery). These should all be included in the endpoint of "non-CNS systemic embolization." Unusual locations for venous thrombosis have also been reported in association with COVID-19 such as thrombosis of the cerebral veins or sinuses. These will be captured under "symptomatic VTE".

The analysis of study efficacy endpoint events will be based on the qualified investigator's assessment in a blinded fashion using standardized event definitions. The EMR and/or eCRF will serve as supporting source records to document the endpoint and to verify or confirm study endpoints.

SAFETY EVALUATIONS

Safety assessments will include monitoring of serious adverse events, nonserious adverse events that are severe or of particular interest and study safety endpoints (major bleeding, including critical site bleeding and fatal bleeding, and nonmajor clinically relevant bleeding).

Additionally, participant-reported adverse events at the virtual study visits that are serious will be collected and assessed by Janssen Global Medical Safety (GMS) per the sponsor's standard operating procedure. Efficacy and safety endpoints including all bleeding events will not be considered as adverse events or serious adverse events. Safety evaluations will be assessed and reported by the investigator per the SoA. Review of the eCRF, EMR, claims databases and/or Social Security Death Index or other source documents may be utilized for data collection.

Bleeding Events

The study will use the ISTH bleeding event classification to assess overt bleeding as major, nonmajor clinically relevant, or trivial.

The safety endpoints for this study include major, critical site and fatal bleeding, and nonmajor clinically relevant bleeding as assessed by a qualified investigator and reported in the eCRF.

An ISTH major bleeding event is defined as overt bleeding that is associated with:

- A fall in hemoglobin of 2 g/dL or more, or
- A transfusion of 2 or more units of packed red blood cells or whole blood, or

- A critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or
- A fatal outcome

Nonmajor clinically relevant bleeding is defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study intervention, or associated with discomfort for the participant such as pain or impairment of activities of daily life. Refer to Appendix 4, Nonmajor Clinically Relevant Bleeding Event Criteria for examples of nonmajor clinically relevant bleeding.

Trivial bleeding is defined as any other overt bleeding episode that does not meet the ISTH criteria for major bleeding or nonmajor clinically relevant bleeding.

The Cunningham protocol may also be applied to automated health plan data to identify and classify bleeding events (Cunningham 2011) as an exploratory endpoint.

STATISTICAL METHODS

Summaries by treatment 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 the statistical analysis plan (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 interpreted 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%.

Sample Size Determination

This is an event-driven study. The targeted total number of primary efficacy outcome events is 333, based on the 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 hazard ratio [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 a 1:1 ratio. This estimate is based on an estimated placebo incidence rate of the primary efficacy outcome of 10%.

Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the eConsent
Randomized	All participants who were randomized in the study
Safety	All randomized participants who take at least 1 dose of study intervention

Key Analysis Sets and Analysis Phases

- Intention-to-Treat (ITT): This analysis set consists of all randomized participants who have a signed eConsent.
- Safety: This analysis set is a subset of the ITT analysis set, consisting of participants who receive at least 1 dose of study intervention.
- Up-to-Day-35: This analysis phase includes all data from randomization to Day 35 visit (Day 35+6 days)
- On-treatment: This analysis phase includes all data from randomization to 2 days after the last dose of the study intervention.

Primary Endpoint(s)

The primary 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.

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 versus 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
- Population-level summary: HR of rivaroxaban 10 mg versus placebo, along with the 2-sided 95% CI

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

The primary statistical hypothesis will be tested using a 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 treatment 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 after the adjustment from the interim analysis (IA), then superiority of the study intervention 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.

Secondary 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 in the ITT analysis

set and Up-to-Day-35 analysis phase. The other variable for the analysis of the secondary endpoint is hospitalization or death at Day 35.

Estimands

The estimands for the analysis of the secondary endpoints are the same as for the primary efficacy endpoint except for the hospitalization and all-cause death at Day 35.

The estimand for the analysis of the frequency of participants who are hospitalized or dead at Day 35 is the same as for the primary efficacy endpoint except variable and population-level summary.

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

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.

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, each at alpha of 0.05 (2-sided). The current proposed hierarchy is listed below. This may be updated/altered in the final SAP rather than requiring a protocol amendment. If an individual test during any step is not statistically significant, subsequent tests will not be declared to be statistically significant:

- 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
- All-cause mortality

Tertiary/Exploratory Endpoint(s)

Each exploratory outcome will be summarized by treatment groups based on the ITT analysis set and Up-to-Day-35 analysis phase.

Safety Analyses

All safety analyses will be made on the Safety Population.

Bleeding Outcomes

The principal safety outcome will be analyzed based on time from randomization to the first occurrence of fatal bleeding and critical site bleeding. Treatments will be compared using the same Cox proportional hazards model as that 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 intervention received. If a participant inadvertently receives both drugs, the participant will be analyzed as in the rivaroxaban group. The ISTH major, nonmajor clinically relevant, and trivial bleeding events will be

analyzed as described for the principal safety outcome. Major bleeding may also be assessed in an exploratory fashion using the Cunningham protocol (Cunningham 2011).

Adverse Events

The verbatim terms used in the EMR and/or eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any adverse event 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. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an adverse event, who have a major bleeding event or who experience a serious adverse event not captured as an endpoint.

Other Analyses

An IDMC will be established for this study.

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 (eg, urgent care visits).

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

Benefit-Risk Analyses

The benefit-risk profile of rivaroxaban versus placebo will be evaluated based on the excess number of events between treatments for events intended to be prevented (benefits) and events that may be caused (risks). Excess number of events is defined as the difference in event rate times in a hypothetical population size (eg, 10,000 participants). To have a comprehensive benefit-risk evaluation, several comparisons will be considered. One analysis will be based on a comparison between the primary efficacy outcome and fatal and critical site bleeding. This analysis phase includes all data from randomization up to Day 35 (inclusive), which is the period of treatment. In addition, the benefit-risk balance may be further assessed for other efficacy outcomes in relation to major bleeding, while potentially taking into consideration the clinical importance of those events, eg, in the context of irreversible harm. The Kaplan-Meier method will be used to display and evaluate the benefits and risks over time.

Interim Analysis

An IA for futility or overwhelming superiority will be conducted when approximately 167 participants with a 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, alpha=0.003) to stop the study early for the overwhelming 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). The detailed rules about stopping the study early will be specified in the SAP.

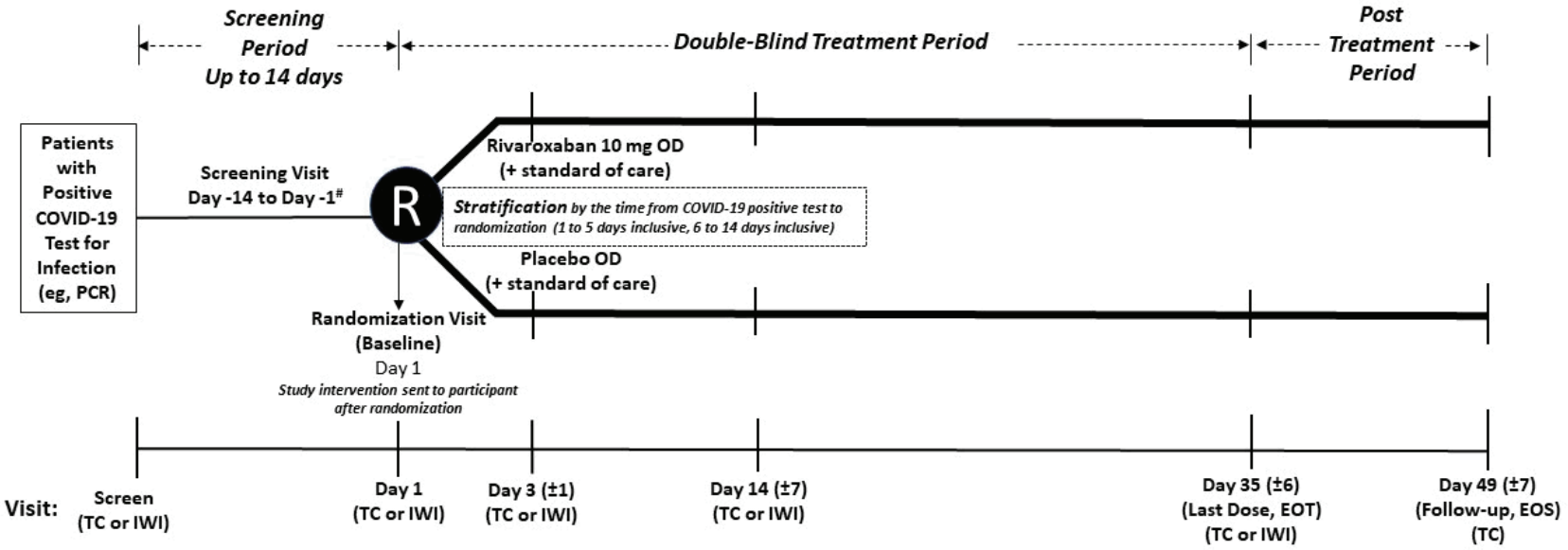
1.2. Schema

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], thrombophilia, 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, non-CNS 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; CNS=central nervous system; 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; PCR=polymerase chain reaction; PE=pulmonary embolism; TC=telephone contact; VTE=venous thromboembolic events

1.3. Schedule of Activities (SoA)

Period	Screening[a]	Double-Blind Treatment[b, a]				Posttreatment[a]	
	Day -14 to Day -1[c] TC or IWI	**Day 1** TC or IWI	**Day 3 (±1 day)** TC or IWI	**Day 14 (±7 days)** TC or IWI	**Day 35 (±6 days) EOT** TC or IWI	**Day 49 (±7 days) EOS** TC	Notes
Screening/Administrative							
Informed consent[d]	X						Must be signed before first study-related activity. May be conducted electronically.
Confirm that participant is known to health system	X						Must have at least 1 record in EMR prior to screening.
Demographics and Medical History	X						
Inclusion/exclusion criteria	X						Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Section 10.5.9, Source Documents of Appendix 5, Regulatory, Ethical, and Study Oversight Considerations.
Record date of positive COVID-19 test documenting infection (eg, PCR test)[e]	X						Participants must be enrolled within 14 days of the first positive COVID-19 PCR test in the event that multiple positive tests are present in the EMR.
Record date of onset of COVID-19 related symptoms	X						

Period	Screening[a]	Double-Blind Treatment[b, a]				Posttreatment[a]	
	Day -14 to Day -1[c] TC or IWI	**Day 1** TC or IWI	**Day 3 (±1 day)** TC or IWI	**Day 14 (±7 days)** TC or IWI	**Day 35 (±6 days) EOT** TC or IWI	**Day 49 (±7 days) EOS** TC	Notes
Record D-dimer level	X						Strong preference to obtain D-dimer in all enrolled participants but may still be enrolled if not able to obtain as long as at least 1 other risk factor present. Date of D-dimer test should be within 14 days (ie, ±14 days) of the date of COVID-19 positive test for infection (eg, PCR).
Contact study participant to communicate COVID-19 / D-dimer status and eligibility	X						
Study Intervention Administration							
Randomization		X[c]					
Confirm participant received study intervention and record date of first dose			X				
Check treatment compliance[f]			X	X	X		
Efficacy Evaluations							
Assessment of symptoms		X	X	X	X	X	Study personnel will systematically question participants about any new or worsening symptoms suggestive of a study endpoint. Participants expressing symptoms suggestive of a study endpoint will be referred to a local physician or ER for evaluation

Period	Screening[a]	Double-Blind Treatment[b, a]				Posttreatment[a]	
	Day -14 to Day -1[c] TC or IWI	**Day 1** TC or IWI	**Day 3 (±1 day)** TC or IWI	**Day 14 (±7 days)** TC or IWI	**Day 35 (±6 days) EOT** TC or IWI	**Day 49 (±7 days) EOS** TC	Notes
Endpoint Assessments[g]		X	X	X	X	X	
Safety Evaluations							
Height	X						Height and body weight will be assessed and reported by participants or obtained from the EMR.
Body Weight	X						
Adverse Events	X	X	X	X	X	X	Serious Adverse Events will be reported from the time a signed and dated eConsent is obtained until completion of the study, as modified in the protocol.
Clinical Laboratory Tests							No routine laboratory testing will be required for the protocol. However, all testing available in the EMR may be utilized to assess efficacy and safety outcome events including adverse events.
Other Assessments							
World Health Organization Research & Development Blueprint: Novel Coronavirus Scale assessment	X	X	X	X	X	X	
Ongoing Review							
Concomitant therapy	X	X	X	X	X	X	Additional information regarding new COVID-19 therapies and/or possible interactions with rivaroxaban may be provided to investigators outside the protocol.

Period	Screening[a]	Double-Blind Treatment[b, a]				Posttreatment[a]	
	Day -14 to Day -1[c] TC or IWI	**Day 1** TC or IWI	**Day 3 (±1 day)** TC or IWI	**Day 14 (±7 days)** TC or IWI	**Day 35 (±6 days) EOT** TC or IWI	**Day 49 (±7 days) EOS** TC	Notes
Medical Resource Utilization		→	→	→	→	X	MRU will be captured through Day 49 and include encounters such as ER visits, hospitalizations, and duration of hospitalization, days in ICU, and other utilization of medical resources (eg, such urgent care visits or days on a ventilator).

a. In-person visit (s) may replace remote contact (s) (Telephone or Interactive Web Interface).
b. If the participant permanently discontinues study intervention prior to Day 35, the participant will continue to be followed according to the contact schedule to complete the final study contact at Day 49.
c. Screening and randomization may occur on the same day (ie, Day 1)
d. At the time of informed consent, 2 alternative means of contact for each participant will be collected (eg, contact information of the participant's children, spouse, significant other, caretaker, legal representative, health care professional).
e. In the event that multiple positive COVID-19 positive PCR tests are present, please record only the date of the first positive test.
f. The study personnel will question the participant about dates of missed dose of study intervention and/or start and stop dates.
g. Study endpoints will be assessed and reported by a qualified investigator according to protocol-specified definitions.

COVID-19=coronavirus disease 2019; EMR=electronic medical record(s); EOS=end of study; EOT=end of treatment; ER=emergency room; ICU=intensive care unit; IWI=Interactive Web Interface; MRU=medical resource utilization; PCR= polymerase chain reaction; TC=telephone call

2. INTRODUCTION

Rivaroxaban is an oral, direct-acting, Factor Xa (FXa) inhibitor anticoagulant that inhibits thrombus generation and thrombus formation. Rivaroxaban has been under development for the treatment of multiple thrombosis-mediated conditions. Rivaroxaban is marketed under the trade name XARELTO® and is approved for multiple indications worldwide. The clinical development program for rivaroxaban is extensive. Almost 200,000 participants have been studied from Phase 1 through multiple large Phase 4 studies as of 15 September 2019, covering several indications and potential indications in the overall clinical development program, including 115,000 participants who received rivaroxaban. For the most comprehensive nonclinical and clinical information regarding rivaroxaban, refer to the latest version of the Investigator's Brochure (IB 2020) for rivaroxaban.

The term "rivaroxaban" throughout the protocol, refers specifically to the brand name XARELTO.

The term "study intervention" throughout the protocol, refers to rivaroxaban or placebo as defined in Section 6.1, Study Interventions Administered.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

The term "participant" throughout the protocol refers to the common term "subject".

2.1. Study Rationale

Coronavirus disease 2019 (COVID-19) has become a pandemic associated with a high case fatality rate (ACC 2020). Early reports have demonstrated that the disease is associated with a coagulopathy in up to approximately 40 to 50% of patients as evidenced by elevation of D-dimer (Tang 2020a, Tang 2020b), which has been associated with more severe disease, the development of acute respiratory distress syndrome (ARDS), disseminated intravascular coagulopathy (DIC), and death (Zhou 2020). A meta-analysis of 4 studies has suggested that an elevated D-dimer in COVID-19 patients is associated with a 3-fold increased risk of severe disease (Lippi 2020). In 1 series of hospitalized patients with severe COVID-19 pneumonia without thromboprophylaxis, the incidence of deep vein thrombosis (DVT) was 25% (Cui 2020). Several subsequent series have demonstrated a high incidence of venous thromboembolism (VTE), which includes DVT or pulmonary embolism (PE) in hospitalized COVID-19 patients even when thromboprophylaxis is given (Klok 2020, Llitjos 2020). One retrospective study suggested that treatment with 7 days or more of thromboprophylaxis was associated with a lower mortality in patients with a D-dimer >6 times (x) the upper limit of normal (Tang 2020a, Tang 2020b). In an Italian series of 388 COVID-19 positive patients consecutively admitted to the hospital, despite all intensive care unit (ICU) patients receiving thromboprophylaxis and 75% of general ward patients receiving thromboprophylaxis, the overall incidence of arterial or venous thromboembolic events was 7.7% (Lodigiani 2020). Younger COVID-19 patients have been reported with ischemic stroke (Oxley 2020), and other patients with deterioration in oxygenation have been reported with at least transient improvement in ARDS with the use of fibrinolytic therapy (Wang 2020), suggesting that

some of the problem in oxygenation could be due to pulmonary thrombi. It has been hypothesized that viral infection and the subsequent inflammatory response may lead to in situ microthrombi in the lung in addition to pulmonary emboli from the extremities. This has now been observed in several autopsy series that have reported both microthrombi and pulmonary emboli in a significant proportion of patients (Ackermann 2020, Lax 2020, Menter 2020, Wichmann 2020).

It is now clear that COVID-19 infection is accompanied by a significant coagulopathy in a significant proportion of patients and that the consequences may lead to both arterial and venous thromboemboli as well as in situ pulmonary thrombosis. Many of these complications are likely to lead to hospitalization and may rapidly progress to worsening pulmonary function, ARDS, the need for ventilation, DIC and death. It is also clear that thromboprophylaxis is warranted when a patient is hospitalized and is recommended in at least 3 guidelines (American College of Cardiology [ACC], World Health Organization [WHO], and the International Society on Thrombosis and Hemostasis [ISTH]) (ACC 2020, Thachil 2020, WHO 2020). However, the coagulopathy in many of these patients is already advanced at the time of admission and anticoagulation may not reverse some of the pathology. It is hypothesized that earlier administration of thromboprophylaxis soon after the diagnosis of COVID-19 prior to hospitalization may reduce the risk of venous and arterial thrombotic complications and may reduce the need for hospitalization and subsequent morbidity and mortality.

In a large series of 4,103 patients testing positive for COVID-19 in New York, 48.7% were hospitalized. Risk factors for hospitalization included older age, obesity, and a history of heart failure, while risk factors for critical illness included a low oxygen saturation and an elevated D-dimer among others (Petrilli 2020). More recent data would suggest that the rate of hospitalization is currently approximately 10% in a large New York Heath Network (Spyropoulos, personal communication).

In this study, we propose to evaluate whether rivaroxaban, an oral FXa inhibitor, when self-administered by the participant within 14 days of diagnosis of COVID-19 in the outpatient setting, can reduce the time to the first occurrence of venous and arterial thrombotic events, hospitalization, and death when self-administered as 10 mg once daily for 35 days.

2.2. Background

Hospitalized COVID-19 patients are currently recommended for thromboprophylaxis as "acute, medically ill" patients per guidelines from ACC, WHO, and the ISTH (Driggen 2020, Spyropoulos 2020, Thachil 2020, WHO 2020). Rivaroxaban is approved in the United States for the prophylaxis of VTE in hospitalized acute, medically ill patients who are at risk for VTE and at low risk for bleeding. Hospitalized COVID-19 patients are an example of such medically ill patients. Hospitalized ICU patients with COVID-19 have a high rate of DVT without thromboprophylaxis (Cui 2020) and have high rates despite low molecular weight heparin (LMWH) thromboprophylaxis (approximately 25% to 40%) (Klok 2020, Spyropoulos personal communication). Patients with COVID-19 infection may not be hospitalized when they might otherwise have been due to low availability of hospital beds or a desire to limit exposure of less acutely ill COVID-19 patients to hospital personnel. Patients with COVID-19 infection may be

relatively immobile at home and are likely at risk for VTE, especially if their D-dimer level is elevated (Lodigiani 2020, Tang 2020a, Tang 2020b). Patients with COVID-19 infection appear to be at increased risk for arterial thrombotic events as well (Bikdeli 2020). Low molecular weight heparin (LMWH) prophylaxis, while preventing VTE, may also decrease thrombin generation and modify the course of DIC. Very preliminary results suggest a favorable effect from LMWH prophylaxis (Bikdeli 2020). Finally, a study of 83 COVID-19 patients suggests that when LMWH prophylaxis was initiated on hospital admission, progression to DIC was rare (Fogarty 2020).

No current guidelines recommend thromboprophylaxis prior to hospitalization in COVID-19 patients, but venous and arterial thrombotic complications have been reported developing suddenly in the outpatient setting. It is hypothesized that starting thromboprophylaxis early after infection is diagnosed, may decrease thrombotic complications, reduce in situ pulmonary microthrombi, maintain better oxygenation, and reduce the need for hospitalization and ultimately reduce mortality.

Rivaroxaban 10 mg once daily is currently indicated in the United States for the prophylaxis of VTE and VTE-related death during hospitalization and post-hospital discharge in adult patients admitted for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE and not at high risk of bleeding. This study will evaluate whether pre-hospital administration of rivaroxaban to symptomatic COVID-19 patients at risk for venous and arterial thrombotic complications may reduce their occurrence, the need for hospitalization or death.

Approved Indications

Rivaroxaban is approved in the United States for the following indications:

- to reduce risk of stroke and systemic embolism in nonvalvular atrial fibrillation
- for treatment of DVT
- for treatment of PE
- for reduction in the risk of recurrence of DVT or PE
- for the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery
- to reduce the risk of major cardiovascular events in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD)
- for prophylaxis of VTE in acutely ill medical patients

Efficacy/Safety Studies

The efficacy and safety of rivaroxaban for prophylaxis of VTE in acutely ill medical patients at risk for thromboembolic complications was evaluated in the MAGELLAN study (Cohen 2013). MAGELLAN was a randomized study to compare the efficacy and safety of extended thromboprophylaxis in hospitalized medical patients with rivaroxaban 10 mg once daily for 35±4 days versus standard of care with enoxaparin 10 ± 4 days followed by placebo. Rivaroxaban was

noninferior to enoxaparin and superior to placebo for reducing the risk of VTE but was associated with more than a 2-fold increased risk of bleeding. Subsequent analyses identified 5 key risk factors associated with the increase in bleeding, namely a history of bronchiectasis, pulmonary cavitation, or pulmonary hemorrhage, active cancer (ie, undergoing acute, in-hospital cancer treatment), active gastroduodenal ulcer in the 3 months prior to treatment, history of bleeding in the 3 months prior to treatment, or dual antiplatelet therapy. Excluding such patients from the MAGELLAN population lead to a subpopulation with preserved efficacy but reduced bleeding (Spyropoulos 2019). Based on these analyses, the Food and Drug Administration (FDA) approved the use of rivaroxaban in medically ill patients at risk for VTE but not at high risk for bleeding for 31 to 39 days of treatment.

2.3. Dose Rationale

The selection of a dose of 10 mg once daily of rivaroxaban is based primarily on the results of the MAGELLAN (Cohen 2013) and MARINER (Spyropoulos 2018) studies conducted for prophylaxis of VTE in acutely ill medical patients at risk for thromboembolic complications not at high risk of bleeding. This dose is also approved for the prevention of VTE after hip and knee surgery and for secondary prevention after 6 months of initial treatment in patients requiring longer treatment based on the results of the EINSTEIN CHOICE study (Weitz 2017). Lower doses have previously been explored in Phase 2 and in the MARINER study (7.5 mg once daily) and were found to not be effective (Spyropoulos 2018). Hence, it is anticipated that 10 mg once daily is likely to be the lowest effective dose for the prevention of VTE. In the EINSTEIN CHOICE study, 20 mg once daily was also evaluated with similar efficacy but with increased bleeding. Finally, in the COMPASS study, a dose of 2.5 mg twice daily was utilized in addition to acetylsalicylic acid (ASA) compared to ASA alone (Eikelboom 2017) and was demonstrated to reduce the incidence of cardiovascular death, myocardial infarction (MI), and stroke but was associated with an increase in major bleeding. A dose of 5 mg twice daily without ASA was also tested and did not significantly reduce the primary endpoint compared with ASA alone but was associated with an increase in major bleeding. The dose of 5 mg twice daily has a similar trough as 20 mg once daily. The dosing regimen of 2.5 mg twice daily provides a similar trough level as rivaroxaban 10 mg once daily. Therefore, based on all of these considerations, the dose of 10 mg once daily has been chosen to optimize the benefit-risk profile in COVID-19 participants in this study.

2.4. Benefit-Risk Assessment

The benefit-risk profile of rivaroxaban versus placebo will be evaluated based on the excess number of events between treatments for events intended to be prevented (benefits) and events that may be caused (risks). Excess number of events is defined as the difference in event rate times a hypothetical population size (eg, 10,000 participants). To have a comprehensive benefit-risk evaluation, several comparisons will be considered. One analysis will be based on a comparison between the primary efficacy outcome (the composite of symptomatic VTE, MI, ischemic stroke, acute limb ischemia, noncentral nervous system (non-CNS) systemic embolization, all-cause hospitalization, and all-cause mortality) and the outcome of fatal and critical-site bleeding. This analysis phase includes all data from randomization to Day 35 (inclusive), which is the period of treatment. In addition, benefit-risk balance may be further assessed for secondary efficacy

outcomes in relation to major bleeding, while potentially taking into consideration the clinical importance of those events. Additional details for benefit-risk analysis will be specified in the statistical analysis plan (SAP).

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints[a]
Primary (Intention-to-Treat [ITT] Population)	
The primary objective will be 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 with placebo in outpatients with acute, symptomatic COVID-19 infection	The primary efficacy outcome variable will be the time to first occurrence of a composite endpoint of symptomatic venous thromboembolism (VTE), myocardial infarction (MI), ischemic stroke, acute limb ischemia, noncentral nervous system (non-CNS) systemic embolization, all-cause hospitalization, and all-cause mortality up to Day 35
Secondary (ITT Population)	
To evaluate whether rivaroxaban reduces the risk of all symptomatic VTE, major arterial thrombotic events (MI, ischemic stroke, acute limb ischemia, non-CNS systemic embolization) and all-cause mortality in outpatients with acute, symptomatic COVID-19 infection	Time to first occurrence of a composite endpoint of symptomatic VTE, MI, ischemic stroke, acute limb ischemia, non-CNS systemic embolization, and all-cause mortality up to Day 35
To evaluate whether rivaroxaban reduces all-cause hospitalization	Time to first occurrence of all-cause hospitalization up to Day 35
To evaluate whether rivaroxaban reduces the risk of symptomatic VTE	Time to first occurrence of symptomatic VTE up to Day 35
To evaluate whether rivaroxaban reduces the need for emergency room (ER) visits	Time to first occurrence of an ER visit up to Day 35
To evaluate whether rivaroxaban reduces the risk of venous and arterial thrombotic events and all-cause hospitalization	Time to first occurrence of symptomatic VTE, MI, ischemic stroke, acute limb ischemia, non-CNS systemic embolization, and all-cause hospitalization up to Day 35
To evaluate whether rivaroxaban reduces the percentage of participants who are hospitalized or dead on Day 35	Incidence of participants who are hospitalized or dead from any cause on Day 35
To evaluate whether rivaroxaban reduces all-cause mortality up to Day 35	Time to all-cause mortality up to Day 35

Objectives	Endpoints[a]
Safety Endpoints (Safety Population)	
To evaluate whether rivaroxaban is associated with an increase in critical site and fatal bleeding	Time to first occurrence of International Society on Thrombosis and Hemostasis (ISTH) critical site and fatal bleeding on treatment (+2 days)
To evaluate whether rivaroxaban is associated with an increase in major bleeding	Time to first occurrence of ISTH major bleeding on treatment (+2 days)
To evaluate whether rivaroxaban is associated with an increase in nonmajor clinically relevant bleeding	Time to first occurrence of nonmajor clinically relevant bleeding on treatment (+2 days)
Tertiary/Exploratory (ITT Population)	
To evaluate whether rivaroxaban improves participant status (eg, prevents worsening of WHO Research and Development Blueprint: Novel Coronavirus Scale for Clinical Improvement) over time	WHO Research and Development Blueprint: Novel Coronavirus Scale for Clinical Improvement over time
To evaluate if rivaroxaban reduces individual component events of the primary efficacy endpoint	Time to first occurrence of a component event of the primary efficacy endpoint (MI, ischemic stroke, acute limb ischemia, and non-CNS systemic embolization) up to Day 35
To evaluate the ability of rivaroxaban to prevent the decline in oxygenation at rest or with ambulation	• The incidence of participants achieving an oxygen saturation (O_{2sat}) below 92% on room air at rest or with ambulation up to Day 35 • The incidence of participants achieving an O_{2sat} below 88% on room air at rest or with ambulation up to Day 35
To evaluate whether rivaroxaban can reduce the need for supplemental oxygen	The incidence of participants requiring supplemental oxygen up to Day 35
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	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) or all-cause mortality (WHO 8) up to Day 35
To evaluate whether rivaroxaban can prevent the occurrence of acute renal failure	The incidence of participants requiring dialysis or having an estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2 on 2 measurements more than 24 hours apart up to Day 35

Objectives	Endpoints[a]
To evaluate whether rivaroxaban can prevent the occurrence of DIC	Time to first occurrence of DIC up to Day 35
To evaluate whether rivaroxaban can prevent the occurrence of ARDS	Time to first occurrence of ARDS up to Day 35
To evaluate whether rivaroxaban can prevent the occurrence of COVID digit	The incidence of occurrence of COVID digit up to Day 35
Collect medical resource utilization (MRU) data	MRU data over time
Benefit-Risk	
To evaluate the benefit-risk profile of rivaroxaban by evaluating the risk differences for key efficacy and safety endpoints through Day 35	Evaluate the risk differences for the composite and components of the primary efficacy outcome compared with fatal and critical site bleeding through Day 35

a. Study endpoints will be assessed and reported by a qualified investigator according to protocol-specified definitions.

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

HYPOTHESES

The primary hypothesis of this study is that rivaroxaban is superior to placebo in the prevention of major venous and arterial thrombotic events, hospitalization, and death in outpatients with acute, symptomatic COVID-19 infection during the treatment period (Day 35). 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 at Day 35, and all-cause mortality.

4. STUDY DESIGN

4.1. Overall 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, with 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 involving a centralized study staff, as well as decentralized nonstudy physicians or nonstudy healthcare providers. There are no required in-person clinic visits required by the study. Participants who complete a COVID-19 test for infection (eg, polymerase chain reaction [PCR] test) as part of standard of care within the health network and who test positive will be identified

by the centralized study staff as potential study participants through review of existing electronic medical records (EMR). Potential study participants may also be recruited by nonstudy physicians in collaboration with the study sites. Participants meeting the eligibility criteria at an in-person or virtual outpatient contact 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 or placebo. At the time of screening, recently taken medications and the need for immediate anticoagulation will be considered to determine if any symptoms reported by study participants are related to a study endpoint at the time of the screening.

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 1 of the strata. In addition, the sponsor will monitor baseline risk factors and may elect to cap enrollment of participants with a certain risk factor to enable an adequate assessment of subgroups with particular risk factors. If a decision is made to institute capping, the site will receive a written communication with instructions for implementation and a request for confirmation of receipt without the need for a protocol amendment.

Study intervention will be shipped or delivered by courier from the drug depot and/or central pharmacy to the participant's address and will be self-administered by the study participant. The study personnel will confirm receipt and initiation of study intervention by remote contact (eg, phone or email), reinforce the study purpose, review dosing instructions, and provide the participant with contact information in the event questions should arise. During the study, the study personnel will contact the participant in accordance with the Schedule of Activities (SoA) to collect specified information, including safety and efficacy outcome events, assess and document the events in the EMR or electronic case report form (eCRF). Study personnel will systematically question participants about any new or worsening symptoms suggestive of a study efficacy or safety endpoint. While assessing the nature and severity of symptoms reported by study participants, careful consideration will be given to symptoms that could be related to manifestations of either COVID-19 or venous and arterial thrombotic events (such as shortness of breath or chest pain) or overt bleeding events and will be encouraged to seek appropriate evaluation by their local health care providers.

At the completion of study intervention treatment (Day 35), the study personnel will contact the participant to confirm vital status and ask about any signs/symptoms or diagnosis of venous and arterial thrombotic events, hospitalization and its duration, bleeding events, serious adverse event collection, and will document the participant's feedback in the EMR or eCRF. The final follow-up will be on Day 49±7 days after randomization. Study intervention 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 intervention or may permanently discontinue study intervention and may receive antithrombotic therapy per institutional guidelines.

Study participants may temporarily interrupt study intervention required for procedures or during evaluation for study endpoints and may be resumed if deemed appropriate by the local physician. All participants should be followed until the last follow-up on Day 49±7 days. In the event that the participant is unavailable (eg hospitalized) or incapacitated (eg 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, EMR or other source records, and information in the eCRF.

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study. Refer to Committees Structure in Appendix 5, Regulatory, Ethical, and Study Oversight Considerations for details.

A diagram of the study design is provided in Section 1.2, Schema.

4.2. Scientific Rationale for Study Design

Blinded, Controlled, Randomized Study

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active intervention with rivaroxaban and to characterize the safety profile relative to a placebo control group. Having a control group is critical for the scientific validity of the study. In a fast-moving pandemic when hospitalization rates may be changing and background therapies may also evolve quickly, having a contemporaneous control group is important to enable valid inferences of statistical comparison across treatment arms. Randomization will be used to minimize bias in the assignment of participants to treatment arms, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment arms, and to enhance the validity of statistical comparisons across treatment arms. Stratification will be done by time from diagnosis. The rationale for this is that it is anticipated that the earlier after the diagnosis, the better the thromboprophylaxis may work. This will ensure balance between treatment groups in participants entering early or later in the course of their disease.

Double-blind intervention will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

Study Population

The goal is to identify a participant population with confirmed, symptomatic COVID-19 disease as defined in Inclusion Criterion #5 (see Section 5.1, Inclusion Criteria) and at least one additional risk factor for venous or arterial thromboembolic disease or more severe pulmonary disease. As all anticoagulants carry some risk of bleeding, these criteria are aimed at enriching the population likely to achieve an endpoint, reducing the risk of a serious bleeding event, while maintaining applicability to a relatively broad population of participants with symptomatic COVID-19 disease.

Choice of Endpoint

Inclusion of all major venous and arterial thrombotic events as part of the primary composite endpoint is based on the pharmacology, mechanism of action, and previous clinical study results

of rivaroxaban. All-cause hospitalization is part of the composite endpoint because it has become clear that the deterioration in lung function in COVID-19 patients is multifactorial and includes evidence of frequent in situ thrombosis in the pulmonary artery vasculature, as well as pulmonary emboli (Lodigiani 2020). Therefore, it is plausible that at least some of the deterioration in lung function and hypoxemia that results in hospitalization may result from ventilation perfusion (V-Q) mismatching associated with reduced flow secondary to pulmonary thrombosis. All-cause death is included in the composite endpoint because of the significance of this outcome in COVID-19 patients and serves as clear measure of net clinical benefit that is easily ascertained and highly relevant for this population.

If treatment with rivaroxaban is successful in lowering the incidence of the primary endpoint, this may result in lower utilization of health services. Therefore, all available data regarding use of medical resource (eg, need for supplemental oxygen therapy, ER visits, ICU days, etc.) will be collected.

Screening Period of 14 Days

The choice of an up to 14-day period to screen potential study candidates who have tested positive for COVID-19 is intended to select for study participants with active disease and at risk for venous and arterial thromboembolic events. The median incubation period of COVID-19 has been reported to be approximately 5 days. Depending on the time interval between symptom onset and when a COVID-19 test is confirmed, the 14-day window for screening is expected to capture a large proportion of participants at risk for major venous and arterial thrombotic events. It is anticipated that rivaroxaban may have increased benefit if administered early after the diagnosis of COVID-19. To ensure balance between treatment groups for those randomized early or later after the diagnosis, the time from diagnosis to randomization will be stratified into the early cohort (Day 1 to 5) and the later cohort (Day 6 to 14). In the event that a participant has multiple COVID-19 positive PCR tests in the EMR, the screening period will begin with the first test, and the date of the first positive test should be recorded in the eCRF.

4.2.1. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue study participation, including new standard-of-care treatments or risks of treatment that may emerge. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled. Participants may be simultaneously enrolled in observational registries of COVID-19 patients. However, 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.

The primary ethical concern is that rivaroxaban may not improve clinical outcomes of a participant with COVID-19. At the present time, there are no guidelines recommending treatment with any antithrombotic therapy prior to hospitalization in COVID-19 participants. Due to the potential for bleeding, there is clinical equipoise as to whether thromboprophylaxis should be initiated prior to hospitalization. All background standard-of-care therapy for COVID-19 may be administered to all study participants as long as no prohibited drug interactions exist. If such a background medication is required, study intervention may be temporarily or permanently discontinued (see Section 4.4, End of Study Definition). Participants may also be simultaneously enrolled in observational registries. Participants may receive therapies for COVID-19 at the discretion of the treating physician if it is part of the standard of care. Participants who wish to participate in another study that is testing an experimental therapy should withdraw from this study. In such a case, passive collection of EMR data and vital status may still be obtained through Day 49.

4.3. Justification for Dose

Refer to Section 2.3, Dose Rationale.

4.4. End of Study Definition

The end of study is considered as the last virtual outpatient contact for the last participant in the study (ie, Day 49 visit of last participant). The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant virtual outpatient contact by the study personnel, in the time frame specified in the Clinical Trial Agreement (refer to the SoA).

Study Completion Definition for Study Participants

A participant will be considered to have completed the study, regardless of whether they continue study intervention treatment, if he or she has completed assessments at Day 49 of the double-blind treatment period, or has experienced a clinical endpoint that precludes further continuation in the study (eg, early mortality). All study participant should have their last follow-up visit at Day 49 regardless of when the last day that study intervention was taken.

Discontinuation of Study Intervention in Study Participants

Participants who prematurely discontinue study intervention for any reason before completion of the double-blind treatment phase should be informed that they are to continue to be followed according to the SoA and can be considered to have completed the study if they have completed the Day 49 assessments.

Consent Withdrawal

- For participants who withdraw consent for follow-up, there should be documentation of the reason for withdrawal. Study staff should explicitly seek information about the possible contribution of efficacy or safety endpoints (including bleeding) or adverse events to the participant's desire to withdraw and document any endpoints or adverse events that are identified in the adverse event section of the eCRF.
- Early permanent discontinuation of study intervention should be distinguished from withdrawal of consent for follow up contacts, or medical records checks. Participants

requesting withdrawal from follow up will no longer be contacted and should be informed that withdrawal of consent for follow up will result in loss of important information about the benefits and risks of study intervention.

5. STUDY POPULATION

Screening for eligible participants will be performed between Day -14 and Day 1. All screening assessments including obtaining informed consent, recording the date of positive COVID-19 test documenting infection, and recording the baseline D-dimer level, if available, which should be obtained within 14 days of the positive COVID-19 test and prior to randomization. SARS-CoV-2 positivity, as determined locally by real time-PCR or any other commercial or public health assay, in any specimen at any time prior to randomization is acceptable and should not be repeated for inclusion in the study. Antibody tests for prior exposure to COVID-19 may not be used for study entry. If all eligibility criteria are met at screening, then randomization may occur on that same day. Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedures are allowed.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator should consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

For a discussion of the statistical considerations of participant selection, refer to Section 9.2, Sample Size Determination.

5.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

1. Male or female (according to their reproductive organs and functions assigned by chromosomal complement)

2. 18 years of age or older

3. COVID-19 positive diagnosis by locally obtained viral diagnostic test (eg, PCR). This may be nasal swab or saliva test or other available technology to demonstrate current infection. (Note: this is not an antibody test or serology test that just indicate prior exposure to the disease. In the case of multiple positive COVID-19 PCR tests, only the date of the first test may be used).

4. Confirm that participant is known to health system, with at least 1 contact in EMR prior to screening

5. Symptoms attributable to COVID-19 (eg, fever, cough, loss of taste or smell, muscle aches, shortness of breath, fatigue)

6. Initial treatment plan does not include hospitalization

7. Presence of at least 1 additional risk factor:

   1) Age ≥60 years

   2) Prior history of VTE

   3) History of thrombophilia

   4) History of CAD

   5) History of PAD

   6) History of cerebrovascular disease or ischemic stroke

   7) History of cancer (other than basal cell carcinoma)

   8) History of diabetes requiring medication

   9) History of heart failure

   10) Body Mass Index ≥35 kg/m^2

   11) D-dimer > upper limit of normal for local laboratory (within 2 weeks of the date of the COVID-19 test and prior to randomization)

8. Must provide consent via eConsent indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study, including follow up

9. Willing and able to adhere to the lifestyle restrictions specified in this protocol

5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

1. Increased risk of bleeding such as 1) significant bleeding in the last 3 months, 2) active gastroduodenal ulcer in the last 3 months, 3) history of bronchiectasis or pulmonary cavitation, 4) need for dual antiplatelet therapy or anticoagulation, 5) prior intracranial hemorrhage, 6) known severe thrombocytopenia (platelet count <50 x 10^9/L), or 7) active cancer and undergoing treatment

2. Any illness or condition that in the opinion of the investigator would significantly increase the risk of bleeding (eg recent trauma, recent surgery, severe uncontrolled

hypertension, gastrointestinal cancer, renal failure requiring dialysis, severe liver disease, known bleeding diathesis)

3. Known allergies, hypersensitivity, or intolerance to rivaroxaban or its excipients (refer to the IB)

4. Positive COVID-19 antibody or serology test after 2-week period of acute, symptomatic COVID-19 infection

5. Known diagnosis of triple positive (ie, positive for lupus anticoagulant, anticardiolipin, and anti-beta 2-glycoprotein I antibodies) antiphospholipid syndrome

6. Recently taken or required to take any disallowed therapies as noted in Section 6.7, Concomitant Therapy before the planned first dose of study intervention or required during the study. For example, the need for the use of strong cytochrome P450 (CYP) 3A4 inhibitor or inducer per local prescribing information

7. Received an investigational intervention (including investigational vaccines) or used an invasive investigational medical device within 30 days before the planned first dose of study intervention or is currently enrolled in an experimental, investigational study (Note: participation in an observational registry is allowed)

8. Women who are pregnant or breastfeeding and women of childbearing potential without proper contraceptive measures. (see Section 10.7, Appendix 7, Contraceptive and Barrier Guidance)

NOTE: The required source documentation to support meeting the enrollment criteria are noted in Section 10.5, Appendix 5, Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the course of the study to be eligible for participation:

1. Refer to Section 6.7, Concomitant Therapy for details regarding prohibited and restricted therapy during the study

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements)

3. Female participants should avoid getting pregnant until the end of the study

4. A woman of childbearing potential must practice a highly effective, preferably user-independent method of contraception (failure rate of <1% per year when used consistently and correctly) and agree to remain on a highly effective method until the end of the study. The investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the dose of

study intervention. Examples of highly effective methods of contraception are located in Section 10.7, Appendix 7, Contraceptive and Barrier Guidance.

5. A male participant must wear a condom when engaging in any activity that allows for passage of ejaculate to another person until the end of the study. Male participants should also be advised of the benefit for a female partner to use a highly effective method of contraception as condom may break or leak.

5.4. Screen Failures

Participant Identification, Enrollment, and Screening

The study will enroll participants from large, integrated, health system networks in the United States. No in-person clinic visits are required for the study.

Potential study participants will be identified based on the following criteria:

- Documented use of health system services as demonstrated by at least 1 contact in EMR prior to screening
- A positive COVID-19 test result (eg, PCR) documented in the EMR

All potential participants who electronically sign the remote e-consent will receive a unique identifier in the eConsent application held by a third-party representative. All data entered and collected via the eConsent application or system are time and date stamped for completeness. Reports will be available to permit a detailed listing of each participant from remote e-consent through the study.

Individuals who are not COVID-19 positive at the time of screening may be rescreened. A participant number will be assigned until rescreened. Participants should not be assigned the same participant number as for the initial screening.

The participant identification and electronic enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent will be used.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Study Interventions Administered

Rivaroxaban will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.

Participants need to receive study intervention preferably within 2 days after randomization.

For details on rescue medications, refer to Section 6.7.1, Rescue Medication. For a definition of study intervention overdose, refer to Section 6.6, Treatment of Overdose.

Description of Interventions

All participants are to self-administer study intervention (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 2 days of randomization if possible. The date and time of the study intervention 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 intervention on Day 35, the participant should discontinue study intervention and complete the Day 35 (±6 days) virtual outpatient contact. A final follow-up visit will occur on Day 49±7 days by virtual outpatient contact as well (refer to the SoA).

All participants will be allowed to be treated with standard of care medications for COVID-19 at the discretion of the participants' local physician. Please see Section 6.7, Concomitant Therapy for drugs with or without significant interactions with rivaroxaban. If a medication must be given to a participant in the study that has an unacceptable drug interaction, the study intervention should be discontinued for as long as the negatively interacting drug must be given. Study intervention may be restarted at the discretion of the investigator if the drug with the negative interaction is discontinued. In the event that the participant wishes to participate in another study that is testing an experimental therapy, the participant should withdraw from this study. However, passive collection of EMR data and vital status may still be obtained through Day 49.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

For rivaroxaban tablets, no storage restrictions (temperature, humidity, light) apply. The storage recommendation for rivaroxaban is at room temperature (approximately 15°C to 30°C).

The drug depot and/or central pharmacy can refer to the pharmacy manual investigational product and procedures manual for additional guidance on study intervention preparation, handling, and storage.

The drug depot and/or central pharmacy is responsible for ensuring that all study intervention received at the depot is accounted for throughout the study. The dispensing of study intervention to the participant must be documented at the drug depot and/or central pharmacy.

Study intervention must be handled in strict accordance with the protocol and the container label and must be stored at the drug depot and/or central pharmacy in a secure area under appropriate environmental conditions.

Study intervention will be delivered to the participant by a qualified member of the drug depot, vendor, central pharmacy, or designee. Study intervention will be supplied only to participants of the study. Participants will be instructed on how to store study intervention and how to destroy any unused study intervention at the end of the 35-day, double-blind treatment period.

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Procedures for Randomization

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 2 intervention groups (rivaroxaban or placebo) based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks in the sites and a stratification factor. The interactive voice response system (IVRS) or interactive web response system (IWRS) will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IVRS/IWRS and will then give the relevant participant details to uniquely identify the participant. The study will be stratified by the time from positive diagnostic of COVID-19 test to first dose into an early cohort (1 to 5 days) and a later cohort (6 to 14 days). The kit number will dictate the study intervention assignment and the matching study intervention bottle to be shipped or delivered to the participant directly from the drug distribution vendor or central pharmacy.

Blinding

The investigator will not be provided with randomization codes. The codes will be maintained within the IVRS or IWRS, which has the functionality to allow the investigator to break the blind for an individual participant.

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. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

Under normal circumstances, the blind should not be broken until all participants have completed the study and the database is finalized. The investigator may in an emergency determine the identity of the intervention by contacting the IVRS/IWRS. While the responsibility to break the intervention code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee if possible, to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented in the source document.

Participants who have had their intervention assignment unblinded should continue to return for scheduled evaluations.

6.4. Study Intervention Compliance

Participants will receive instructions on compliance with study intervention administration at the screening visit and during the course of the study, according to the SoA. Due to health concerns associated with handling unused study intervention from COVID-19 infected participants, the study personnel will assess study intervention compliance by questioning the participant about dates of missed dose of study intervention and/or start and stop dates.

6.5. Continued Access to Study Intervention After the End of the Study

No continued access will be proposed for this study. Participants will be instructed that study intervention will not be made available to them after they have completed/discontinued study intervention and that they should return to their primary physician to determine standard of care.

6.6. Treatment of Overdose

Overdose of rivaroxaban may lead to hemorrhage. Discontinue rivaroxaban and initiate appropriate therapy if bleeding complications associated with overdosage occur. Rivaroxaban systemic exposure is not further increased at single doses >50 mg due to limited absorption. The use of activated charcoal to reduce absorption in case of rivaroxaban overdose may be considered. Due to the high plasma protein binding, rivaroxaban is not dialyzable (see Clinical Pharmacology [Section 12.3] of the United States Prescribing Information [USPI]). Partial reversal of laboratory anticoagulation parameters may be achieved with use of plasma products. An agent to reverse the anti-FXa activity of rivaroxaban is available (Andexanet alpha, Andexxa®). Please see the prescribing information for further details regarding administration.

6.7. Concomitant Therapy

Prestudy therapies administered up to 30 days before first dose of study intervention must be recorded at screening.

Because all the participants enrolled in the proposed study are COVID-19 positive with infection symptoms, they will be managed according to local treatment guidelines, including the latest version of Centers for Disease Control (CDC) Information for Clinicians on Therapeutic Options for Patients with COVID-19. Open or off-label use of agents that are intended to inhibit SARS-CoV-2 viral activity are permitted in the study, including those listed in the CDC guidelines on Therapeutic Options for patients with COVID-19. In the event that a participant wishes to participate in another study that is testing an experimental therapy, the participant should withdraw from this study. However, passive collection of EMR data and vital status may still be obtained through Day 49.

Interactions of Rivaroxaban with COVID-19 Therapies

Based on the European Society of Cardiology Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic (ESC 2020), the interactions of rivaroxaban with

COVID-19 therapies are outlined in Table 1. The list of COVID-19 therapies should not be considered exhaustive. Additional information regarding new COVID-19 therapies and/or possible interactions with rivaroxaban may be provided to investigators outside of the protocol.

Table 1: Interactions of rivaroxaban with COVID-19 therapies

COVID-19 Therapies (impact on rivaroxaban)	**Rivaroxaban** (interaction with COVID-19 therapy)
Chloroquine (up*)	(2) No clinically significant interaction
Hydroxychloroquine (up*)	(2) No clinically significant interaction
Azithromycin (up*)	(3) Potential interaction
Darunavir/Cobicistat (up*)	(4) No coadministration
Atazanavir/Cobicistar (up*)	(4) No coadministration
Lopinavir/Ritonavir (up*)	(4) No coadministration
Ribavirin	(2) No interaction
Remdesivir	(2) No interaction
Favipiravir	(2) No interaction
Bevacizumab	(1) No info
Eculizumab	(1) No info
Tocilizumab (down*)	(2) No clinically significant interaction
Fingolimod	(1) No info
Interferon	(1) No info
Pirfenidone	(1) No info
Methylprednisolone	(1) No info
Nitazoxanide	(2) No interaction

Key:
Up*: potentially increases patient exposure to rivaroxaban;
Down*: potentially decreases patient exposure to rivaroxaban;

(1) No info: No information found
(2) No interaction: No clinically significant interaction is expected, or potential interaction is likely to be of weak intensity, not requiring additional action/monitoring or dose adjustment;
(3) Potential interaction: Potential interaction which may require additional monitoring;
(4) No coadministration: the drugs should not be co-administered.

Source: Adapted from the European Society of Cardiology Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic, Table 16.

Allowed Concomitant Medications

Antiplatelet therapy with a **single** oral agent such as ASA (aspirin) ≤162 mg, dipyridamole, or monotherapy with a chemoreceptor for adenosine diphosphate (P2Y12) inhibitor (ie, clopidogrel ≤75 mg, ticlopidine ≤250 mg, prasugrel or ticagrelor) is allowed. Dual antiplatelet therapy (eg, ASA plus a P2Y12 inhibitor) is not allowed, with the exception of ASA and dipyridamole. All antiplatelet therapy must be recorded throughout the study beginning with start of the first dose of study intervention. Nonsteroidal anti-inflammatory drugs (NSAID) are allowed.

Note: Coadministration of rivaroxaban with ASA, clopidogrel or other P2Y12 inhibitors, or chronic NSAID use may increase the risk of bleeding.

Disallowed Concomitant Medications

Potential participants must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation. If participants require or take prohibited medications during the study as outlined below, they must either temporarily interrupt or permanently discontinue the study intervention, as appropriate for the duration of the therapy with the prohibited medication:

- Combined P-glycoprotein (P-gp) and strong CYP3A4 inhibitors (such as but not limited to ketoconazole, telithromycin or ritonavir, lopinavir, atazanavir/cobicistat, and darunavir/cobicistat) use within 4 days before randomization, or planned use during the study. Itraconazole use is prohibited within 7 days before randomization and during the study.
- Combined P-gp and strong CYP3A4 inducers (such as but not limited to rifampin/rifampicin, rifabutin, rifapentine, phenytoin, phenobarbital, carbamazepine, or St. John's Wort) use within 2 weeks before randomization, or planned use during the study.
- Anticoagulant (eg, warfarin sodium or other vitamin K antagonists, Factor II or Xa inhibitors) is prohibited as concomitant therapy during the study. Study intervention should be discontinued in participants who are hospitalized and receive open-label thromboprophylaxis per guidelines, develop any condition that requires anticoagulation (eg, atrial fibrillation, VTE) that will extend beyond the end of the study intervention treatment phase.
- Use of antiplatelet therapy, including:
  - ASA >162 mg/day
  - Clopidogrel >75 mg/day or ticlopidine >250 mg twice daily
  - Cilostazol >200 mg/day
  - Dual therapy with 2 or more antiplatelet agents (dipyridamole with ASA is permitted)
  - Thrombin-receptor antagonists (eg, vorapaxar)
- Modification of an effective pre-existing therapy should not be made for the explicit purpose of entering a participant into the study.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

6.7.1. Rescue Medication

An agent to reverse the anti-FXa activity of rivaroxaban is available (Andexanet alpha, Andexxa®). Because of high plasma-protein binding, rivaroxaban is not dialyzable (see Clinical Pharmacology [Section 12.3] of the USPI). Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. Use of procoagulant reversal agents, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate, or recombinant factor VIIa, may be considered but has not been evaluated in clinical efficacy and safety studies. Monitoring for the anticoagulation effect of rivaroxaban using a clotting test (prothrombin time [PT], international normalized ratio [INR] or activated partial thromboplastin time [aPTT]) or anti-FXa activity is not recommended. However, measurement of anti-FXa activity using rivaroxaban-specific calibrators and controls correlates closely with plasma concentrations and can be a marker for plasma concentration.

The study site will not be supplied with rescue medication by the sponsor.

6.7.2. Approach to the Subject with a Bleeding Event

If a subject has a serious bleeding event during study intervention, the subject should be referred for evaluation at the appropriate facility such as an urgent care center or emergency department depending on the severity of the bleeding. The following routine measures should be considered:

Delay the next administration of study intervention or discontinue treatment if indicated. Rivaroxaban has a plasma (or terminal elimination) half-life of 5 to 9 hours in healthy young subjects (aged 20 to 45 years) and 11 to 13 hours in elderly subjects (aged 60 to 76 years). Therefore, temporary cessation of study intervention may allow control of bleeding. Unblinding of study intervention should not be necessary.

Consider the usual treatment measures for bleeding events, including fluid replacement and hemodynamic support, blood transfusion, and fresh frozen plasma, if physical examination and laboratory testing suggest benefit could be obtained.

Consider that other causes besides antithrombotic medication can be contributory to the seriousness of the bleeding event (ie, rule out DIC, thrombocytopenia, and other coagulopathies; kidney and liver dysfunction; concomitant medications), and treat accordingly.

If bleeding cannot be controlled by these measures, consider administration of 1 of the following procoagulants (according to the dosages advised in their respective package inserts):

- Activated PCC
- PCC
- Recombinant factor VIIa (NovoSeven®)
- Andexanet alpha (Andexxa)

Any products administered to control bleeding should be entered in the eCRF.

Note: Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. There is currently no scientific rationale for benefit, or experience with systemic hemostatics (eg, desmopressin, aprotinin, and epsilon aminocaproic acid).

After resolution of the bleeding event, restarting study intervention may be considered based on the clinical judgment of the investigator.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A participant's study intervention must be discontinued if:

- The participant withdraws consent to receive study intervention,
- The investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the participant to discontinue study intervention,
- If a participant requires hospitalization for COVID-19 (ie, the combined total of inpatient and/or ER stay ≥24 hours),
- The participant experiences symptomatic VTE, MI, ischemic stroke, acute limb ischemia, non-CNS systemic embolization,
- The participant develops any condition, which in the investigator's judgment requires long-term anticoagulation, thromboprophylaxis, or fibrinolysis,
- The participant develops renal failure requiring dialysis or has an eGFR <15 ml/min/1.73m^2,
- The participant becomes pregnant,
- The participant is required to take a medication known as a strong CYP3A4 inhibitor.

If a participant discontinues study intervention for any reason before the end of the study, assessments should continue in accordance with the SoA with all scheduled visits. If the participant permanently discontinued study intervention prior to Day 14, the Day 35 and Day 49 visits will still occur. Study intervention assigned to the participant who discontinued study intervention may not be assigned to another participant.

7.1.1. Temporary Discontinuation

If a participant is hospitalized for reason(s) not related to COVID-19 illness, has not experienced an event of symptomatic VTE, MI, ischemic stroke, acute limb ischemia, or non-CNS systemic embolization, or bleeding, the participant may be restarted on study intervention after being discharged unless the participant requires post-hospitalization anticoagulation, at the discretion of the investigator.

If the participant requires an invasive procedure or surgery as an outpatient, study intervention should be stopped at least 24 hours before the procedure to reduce the risk of bleeding. In deciding whether a procedure should be delayed until 24 hours after the last dose of study intervention, the increased risk of bleeding should be weighed against the urgency of the procedure. Study

intervention may be restarted after the surgical or other procedures once adequate hemostasis has been established, if deemed appropriate by the local treating physician.

Participants hospitalized for worsening of COVID-19 disease should temporarily discontinue study intervention during the hospitalization as guidelines now recommend thromboprophylaxis in most patients who do not have a contraindication. After discharge, study intervention may be restarted. However, if it is the policy of the hospital to routinely provide anticoagulation after hospital discharge, then study intervention should be permanently discontinued.

7.2. Participant Withdrawal From the Study

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent

In the event a participant withdraws consent and does not agree to any kind of follow-up and specifically refuses any further contact with study staff, this must be documented in the study database. Vital status may be obtained at study end through the participant's physician, medical claims, alternate contacts (eg, family and/or friends) or public information according to local guidelines and as allowed by local regulations.

Participants in the study may participate in an observational registry without need for withdrawal from the study. Participants wishing to enter another investigational study must withdraw from this study. However, passive collection of EMR data and vital status through the end of this study (Day 49) will still be obtained even if the participant withdraws from the study to participate in another investigational study.

Withdrawal of Consent

A participant declining to continue with scheduled virtual outpatient contacts does not constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the eConsent may be utilized (eg, consult with family members, contacting the participant's other physicians, medical records, database searches, use of locator agencies at study completion,) as local regulations permit. For participants who withdraw consent for any kind of follow-up, the participant's vital status will be obtained through applicable information sources according to local guidelines and as allowed by local regulations. Passive collection of EMR data will continue to be allowed unless consent for the use of this EMR data is specifically withdrawn by the participant.

Withdrawal of consent should be an infrequent occurrence in clinical studies (Rodriguez 2015). Therefore, prior to the start of the study, the sponsor and the investigator should discuss and reach a clear understanding of what constitutes withdrawal of consent in the context of the available reduced follow-up mechanisms listed.

7.3. Lost-to-Follow up

To reduce the chances of a participant being deemed lost-to-follow up, attempts should be made prior to randomization to obtain contact information from each participant, eg, home, work, and mobile telephone numbers and email addresses for both the participant as well as appropriate family members.

A participant will be considered lost-to-follow up if he or she repeatedly is unable to be contacted by the study personnel or the status cannot be verified based on the participant's medical record. A participant cannot be deemed lost-to-follow up until all reasonable efforts made by the study personnel to contact the participant are deemed futile. The following actions should be taken if a participant cannot be reached at a scheduled point of contact:

- The study personnel should attempt to contact the participant to reschedule the missed virtual outpatient contact as soon as possible, to counsel the participant on the importance of maintaining the schedule of virtual outpatient contacts, to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost-to-follow up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, e-mails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods). Locator agencies may also be used as local regulations permit. These contact attempts should be documented in the participant's medical records.

Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

Study personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost-to-follow up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Should a study site close, eg, for operational, financial, or other reasons, and the investigator cannot reach the participant to inform them, their contact information will be transferred to another study site.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The SoA summarizes the frequency and timing of efficacy, MRU, benefit-risk, health economic, and safety measurements applicable to this study.

Medical resource utilization and health economics data will be collected. Refer to Section 8.4, Medical Resource Utilization and Health Economics for details.

No blood collection will be required.

Study-Specific Materials

The investigator will be provided with the following supplies including but not limited to:

- IB
- IWRS Manual
- Sample eConsent
- Contact Information Page(s)
- Electronic Data Capture (eDC) Manual

8.1. Efficacy Assessments

Efficacy outcomes will be assessed and documented per the SoA and will include all information necessary for the following key efficacy outcomes to be assessed via telephone/web contact, from review of the eCRF, EMR, claims databases, Social Security Death Index, or other source documents: all-cause mortality (and cause of death if known), all-cause hospitalization, MI, stroke (ischemic, hemorrhagic, unknown etiology), acute limb ischemia, non-CNS systemic embolization, symptomatic VTE (ie, symptomatic DVT, and PE).

Any event that includes symptoms or signs suggestive of symptomatic VTE events, MI, ischemic stroke, acute limb ischemia, or non-CNS systemic embolization will be assessed and entered into the eCRF as a potential event by the investigator/study team. In identifying potential events, investigators are encouraged to give careful consideration to symptoms that may represent manifestations of major venous and arterial thrombotic events and encourage participants to seek medical care. Review of EMR data for health system encounters suggestive of study events (eg, hospitalizations) may also be conducted to identify study endpoints. Source documents may be requested from nonstudy physicians within the health network or from health care encounters outside of the investigator's health network to assist in identifying all efficacy and safety outcome events.

There will be no independent adjudication by a Clinical Events Committee. Potential events will be adjudicated locally by a qualified site investigator who will review source documents, such as the EMR, eCRF, and other study records or source documents in a blinded and impartial manner to verify/adjudicate events according to the endpoint definitions in Section 10.3, Appendix 3, Endpoint Definitions. The qualified investigator will evaluate all available information from the eCRF, EMR or other source documents and will document in the eCRF whether the subject did or did not have any of the following events according to the protocol-specified definitions of the events:

- Symptomatic VTE
- MI
- Stroke (ischemic, hemorrhagic or unknown etiology)
- Acute limb ischemia

- Non-CNS systemic embolization

Any clinical event that suggests the possibility that an efficacy outcome event has occurred (including acute coronary syndrome and transient ischemic attack) should be recorded in the eCRFs and will be assessed by the investigator. COVID-19 has been associated with emboli in a variety of locations, including internal organs (eg, mesenteric artery, renal artery). These should all be included in the endpoint of "non-CNS systemic embolization." Unusual locations for venous thrombosis have also been reported in association with COVID-19 such as thrombosis of the cerebral veins or sinuses. These will be captured under "symptomatic VTE" per the guidelines in Section 10.3, Appendix 3, Endpoint Definitions.

The analysis of study efficacy endpoint events will be based on the qualified investigator's assessment in a blinded fashion using standardized event definitions. The EMR and/or eCRF will serve as supporting source records to document the endpoint and to verify or confirm study endpoints. Event definitions for verifying or confirming study endpoints are provided in Section 10.3, Appendix 3, Endpoint Definitions. Details regarding the process for identification of events, verification or adjudication of study endpoints against event definitions, and for retaining source documentation not available in the clinical database will be provided in a Site Event Manual. Upon request, all pertinent data outside the clinical database that was used for event verification or adjudication must have all participant-identifying information masked or redacted and made available to the sponsor or designee. Any modifications, clarifications or corrections to endpoint definitions will be noted in the SAP rather than requiring a protocol amendment.

8.2. Safety Assessments

Safety assessments will include monitoring of serious adverse events, nonserious adverse events that are severe or of particular interest and study safety endpoints (major bleeding, including critical site bleeding and fatal bleeding, and nonmajor clinically relevant bleeding).

Additionally, participant-reported adverse events at the virtual study visits that are serious will be collected and assessed by Janssen Global Medical Safety (GMS) per the sponsor's standard operating procedure. Efficacy and safety endpoints including all bleeding events will not be considered as adverse events or serious adverse events (see Section 8.3, Adverse Events, Serious Adverse Events, and Other Safety Reporting). Safety evaluations will be assessed and reported by the investigator per the SoA. Review of the eCRF, EMR, claims databases, and/or Social Security Death Index, or other source documents may be utilized for data collection.

Bleeding Events

The study will use the ISTH bleeding event classification to assess overt bleeding as major, nonmajor-clinically relevant, or trivial.

The safety endpoints for this study include major, critical site and fatal bleeding, and nonmajor clinically relevant bleeding as assessed by a qualified investigator and reported in the eCRF.

An ISTH major bleeding event is defined as overt bleeding that is associated with (Schulmann 2005):

- A fall in hemoglobin of 2 g/dL or more, or
- A transfusion of 2 or more units of packed red blood cells or whole blood, or
- A critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or
- A fatal outcome

Nonmajor clinically relevant bleeding is defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study intervention, or associated with discomfort for the participant such as pain or impairment of activities of daily life. Refer to Section 10.4, Appendix 4, Nonmajor Clinically Relevant Bleeding Event Criteria for examples of nonmajor clinically relevant bleeding.

Trivial bleeding is defined as any other overt bleeding episode that does not meet the ISTH criteria for major bleeding or nonmajor clinically relevant bleeding.

The Cunningham protocol may also be applied to automated health plan data to identify and classify bleeding events (Cunningham 2011) as an exploratory endpoint.

Details regarding the IDMC are provided in Section 10.5.5, Committees Structure of Appendix 5, Regulatory, Ethical, and Study Oversight Considerations.

8.2.1. Physical Examinations

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

8.2.2. Pregnancy Testing

No screening serum pregnancy test will be obtained before the first dose of study intervention on Day 1. Female participants of childbearing potential will be screened for pregnancy status utilizing information from the EMR and if the participant suspects she may be pregnant, the study personnel will encourage that an at home self-pregnancy test be conducted prior to randomization.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

All participant-reported adverse events at the virtual study visits that are serious will be collected and assessed by Janssen GMS per the sponsor's standard operating procedure. Queries for these cases will go to the principal investigator as appropriate. If follow up is needed with the participant's treating physician, it will be done either through the principal investigator or directly with the treating physician. Participants will agree to provide their treating physician's contact information to the study team. All serious adverse events will be assessed by Janssen GMS for potential suspected unexpected serious adverse reactions (SUSARs) for expedited regulatory reporting.

Efficacy and safety endpoints including all bleeding will be captured in the EMR and/or eCRF as endpoints only and will be waived from unblinding and exempt from expedited reporting.

Special Reporting Situations

Safety events of interest on a sponsor study intervention that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Inadvertent or accidental exposure to a sponsor study intervention
- Medication error involving a sponsor product (with or without participant exposure to the sponsor study intervention, eg, name confusion)

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the eCRF.

Non-Serious Adverse Events

The following should be reported in the eCRF:

- Non-serious adverse events leading to permanent study intervention discontinuation.
- All severe nonserious adverse events (regardless of relation to study intervention) will be collected except for study endpoints.
- Any adverse event of particular concern to the investigator may be recorded in the eCRF to alert the sponsor.

Any other nonserious adverse events do not require reporting.

8.3.1. Time Period for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All participant-reported serious adverse events, nonserious adverse events that are severe or of particular interest, and bleeding events will be collected from the time a signed and dated eConsent is obtained until the participant completes their participation on Day 49 of the posttreatment period. All serious adverse events occurring during the study must be reported to the appropriate sponsor contact person by study personnel within 24 hours of their knowledge of the event.

Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all SUSARs. The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee (IEC)/Institutional Review Board (IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified (See Table 2).

Table 2: Reporting of Serious Unexpected and Related Events (Unless Otherwise Requested by Health Authorities or Ethics Committees)

Event Type	Expedited Report to Health Authorities and Investigators	Unblinding to Health Authorities	Unblinding to Investigators
Study endpoint events (including all bleeding)	N	N	N
Non-endpoint serious adverse events	Y	Y	N

Adverse Events as Study Endpoints

All events that are assessed by the investigator as possibly being 1 of the components of the primary composite endpoint, including symptomatic DVT or PE, MI, ischemic stroke, acute limb ischemia, non-CNS systemic embolization, all-cause hospitalization, and all-cause mortality, or a secondary efficacy endpoint or a safety endpoint (ie, major bleeding, critical site bleeding and fatal bleeding and nonmajor clinically relevant bleeding) including all bleeding should be handled as follows.

Investigator Responsibilities:

All confirmed study endpoint events must be reported to the sponsor. Investigators are also required to retain source records used to verify or confirm the outcome of endpoint events if not available in the clinical database. If requested by the sponsor, details on assembly and submission of source records associated with the event will be provided.

Sponsor Responsibilities (or Designee):

To protect the integrity of the study, components of the primary endpoint, secondary endpoints, and bleeding endpoints will **not** be unblinded or reported to either Health Authorities (HAs) or investigators as safety reports unless otherwise requested by HAs or Ethics Committees. After study completion, these events will be included in the final analysis, which will be unblinded and submitted to HAs with the study report.

Refer to Table 2 for a summary of the reporting process for serious unexpected and related events.

8.3.2. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using a serious adverse event reporting form. Participants who become pregnant should permanently discontinue study intervention.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.3.3. Disease-related Events and Disease-related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

The following events are considered COVID-19 infection-related events as per WHO assessment and do not require sponsor reporting to the sponsor and HAs:

Most Common Symptoms:

- Fever
- Dry cough
- Tiredness

Less Common Symptoms:

- Aches and pains
- Sore throat
- Diarrhea
- Conjunctivitis
- Headache
- Loss of taste or smell
- A rash on skin, or discoloration of fingers or toes

Serious Symptoms:

- Difficulty breathing or shortness of breath
- Chest pain or pressure
- Loss of speech or movement

In addition, serious or nonserious adverse events that are known to be associated with COVID-19 (eg, "COVID-19 digits", ARDS, DIC) do not have to be reported as adverse events, but may be captured in the eCRF as endpoints. Symptoms listed above that are reported to study personnel should be evaluated as to whether they might be related to study endpoints such as PE, MI or ischemic stroke. Study participants with such symptoms should be referred to their local physician or ER for evaluation. Study participants with worsening shortness of breath that may represent worsening viral pneumonia should also seek prompt medical attention.

8.4. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data, associated with medical encounters, will be collected in the eCRF or via EMR or from other source documents by the investigator and study personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded. The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Duration of hospitalization (total days length of stay, including duration by wards; eg, ICU)
- Number and character of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters and treatments (including physician or ER visits, tests and procedures, and medications)

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the SAP that will be finalized within 3 months after the first participant is randomized.

9.1. Statistical Hypotheses

The primary hypothesis is to evaluate whether rivaroxaban reduces the risk of a composite endpoint of major venous and arterial thrombotic events, hospitalization and all-cause mortality compared with 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 the negation of the alternative hypothesis, that is, the survival function for the placebo group is not lower than that for the rivaroxaban group. As a further illustration of the hypotheses, for the case where hazard functions are proportional, the above alternative hypothesis can be expressed as that the hazard ratio (HR) of rivaroxaban versus placebo is less than 1, and the null hypothesis is that the HR is at least 1.

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 at Day 35, and all-cause mortality.

9.2. Sample Size Determination

This is an event-driven study. The targeted total number of primary efficacy outcome events is 333, based on the 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%.

9.3. Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the eConsent
Randomized	All participants who were randomized in the study
Safety	All randomized participants who take at least 1 dose of study intervention

Key Analysis Sets and Analysis Phases

- Intention-to-Treat (ITT): This analysis set consists of all randomized participants who have a signed eConsent
- Safety: This analysis set is a subset of the ITT analysis set, consisting of participants who receive at least one dose of study intervention
- Up-to-Day-35: This analysis phase includes all data from randomization to Day 35 visit (Day 35+6 days)

  On-treatment: This analysis phase includes all data from randomization to 2 days after the last dose of the study intervention

9.4. Statistical Analyses

The SAP will be finalized prior to 3 months after the first participant is randomized and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

Summaries by treatment 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 the 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 interpreted 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%.

9.4.2. Primary Endpoint(s)

The primary endpoint is the 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.

Estimand

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

- Population: Medically ill participants 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 versus 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
- Population-level summary: HR of rivaroxaban 10 mg versus placebo, along with the 2-sided 95% CI

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

The primary statistical hypothesis will be tested using a 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 treatment 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 after the adjustment from IA, then superiority of the study intervention 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 cumulative event rate derived from Kaplan-Meier estimate will be displayed graphically to evaluate the treatment effect over time.

Homogeneity of treatment effects will be assessed by subgroups and their interactions with treatment. Pre-specified subgroups and the analysis methods will be detailed in the SAP.

9.4.3. Secondary 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 in the ITT analysis set and Up-to-Day-35 analysis phase. The other variable for the analysis of the secondary endpoint is hospitalization or death at Day 35.

Estimands

The estimands for the analysis of the secondary endpoints are the same as for the primary efficacy endpoint except for the hospitalization and all-cause death at Day 35.

The estimand for the analysis of the frequency of participants who are hospitalized or dead at Day 35 is the same as for the primary efficacy endpoint except variable and population-level summary.

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

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.

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, each at alpha of 0.05 (2-sided). The current proposed hierarchy is listed below. This may be updated/altered in the final SAP rather than requiring a protocol amendment. If an individual test during any step is not statistically significant, subsequent tests will not be declared to be statistically significant:

- 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
- All-cause mortality

9.4.4. Tertiary/Exploratory Endpoint(s)

Each exploratory outcome will be summarized by treatment groups based on the ITT analysis set and Up-to-Day-35 analysis phase.

9.4.5. Safety Analyses

All safety analyses will be made on the Safety Population.

Bleeding Outcomes

The principal safety outcome will be analyzed based on time from randomization to the first occurrence of fatal bleeding and critical site bleeding. Treatments will be compared using the same Cox proportional hazards model as that 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 intervention received. If a participant inadvertently receives both drugs, the participant will be analyzed as in rivaroxaban group. The ISTH major, nonmajor clinically relevant, and trivial bleeding events will be analyzed as described for the principal safety outcome. Major bleeding may also be assessed in an exploratory fashion using the Cunningham protocol (Cunningham 2011).

Adverse Events

The verbatim terms used in the EMR and/or eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any adverse event 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. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an adverse event, who have a major bleeding event or who experience a serious adverse event not captured as an endpoint.

9.4.6. Other Analyses

An IDMC will be established as noted in Section 10.5.5, Committees Structure in Appendix 5, Regulatory, Ethical, and Study Oversight Considerations.

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 (eg, urgent care visits).

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

Benefit-Risk Analyses

The benefit-risk profile of rivaroxaban versus placebo will be evaluated based on the excess number of events between treatments for events intended to be prevented (benefits) and events that may be caused (risks). Excess number of events is defined as the difference in event rate times in a hypothetical population size (eg, 10,000 participants). To have a comprehensive benefit-risk evaluation, several comparisons will be considered. One analysis will be based on a comparison between the primary efficacy outcome and fatal and critical-site bleeding. This analysis phase includes all data from randomization up to Day 35 (inclusive), which is the period of treatment. In addition, the benefit-risk balance may be further assessed for other efficacy outcomes in relation to major bleeding, while potentially taking into consideration the clinical importance of those events, eg, in the context of irreversible harm. The Kaplan-Meier method will be used to display and evaluate the benefits and risks over time.

9.5. Interim Analysis

An interim analysis for futility or overwhelming superiority will be conducted when approximately 167 participants with a 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, alpha=0.003) to stop the study early for the overwhelming superiority. Alpha=0.049 will be used for the final analysis to control the family-wise type I error rate at alpha of 0.05 (2-sided). The detailed rules about stopping the study early will be specified in the SAP.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Definitions

ACC	American College of Cardiology
ARDS	acute respiratory distress syndrome
ASA	acetylsalicylic acid
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CDC	Centers for Disease Control and Prevention
CI	confidence interval(s)
CT	computed tomography
cTn	cardiac troponin
COVID-19	coronavirus disease 2019
CYP	cytochrome P450
DIC	disseminated intravascular coagulopathy
DVT	deep vein thrombosis
EC	Executive Committee
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
eDC	electronic data capture
eGFR	estimated glomerular filtration rate
EMR	electronic medical record(s)
ER	emergency room
ESC	European Society of Cardiology
FDA	Food and Drug Administration
FOIA	Freedom of Information Act
FSH	follicle stimulating hormone
FXa	factor Xa
GCP	Good Clinical Practice
GMS	Global Medical Safety
HA(s)	Health Authority (Authorities)
HR	hazard ratio
HRT	hormonal replacement therapy
IA	interim analysis
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICU	intensive care unit
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Hemostasis
ITT	Intention-to-Treat
IVRS	interactive voice response system
IWRS	interactive web response system
LBBB	left bundle branch block
LMWH	low molecular weight heparin
non-CNS	noncentral nervous system
NSAID	nonsteroidal anti-inflammatory drugs
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MRU	medical resource utilization
O_{2sat}	oxygen saturation
P2Y12	chemoreceptor for adenosine diphosphate
P-gp	P-glycoprotein
PAD	peripheral artery disease

PCC	prothrombin complex concentrate
PCI	percutaneous coronary intervention
PCR	polymerase chain reaction
PE	pulmonary embolism
PQC	Product Quality Complaint
RR	relative risk
RRR	relative risk reduction
RRT	renal replacement therapy
SAP	statistical analysis plan
SoA	Schedule of Activities
ST-T	ST-segment–T wave
SUSAR	suspected unexpected serious adverse reaction
URL	upper reference limit
US	United States
USPI	United States Prescribing Information
V-Q	ventilation-perfusion
VTE	venous thromboembolism
WHO	World Health Organization
x	times

Definitions of Terms

Electronic source system	Contains data traditionally maintained in a hospital or clinic record to document medical care or data recorded in an eCRF as determined by the protocol. Data in this system may be considered source documentation.

10.2. Appendix 2: World Health Organization Research and Development Blueprint: Novel Coronavirus Scale for Clinical Improvement (Draft from WHO 2020)

Patient State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized Mild Disease	Hospitalized, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalized Severe Disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – vasopressors, RRT, ECMO	7
Death		8

10.3. Appendix 3: Endpoint Definitions

For all endpoints, qualified investigators will review all available source documentation available, including information from the eCRF, EMR, Claims data, Social Security Death Index, other source documents to make decisions as to whether or not there is sufficient information, in their clinical judgment to satisfy the definition of each endpoint event as noted below. In certain instances, additional information may be requested if insufficient information is available to make a decision. However, the qualified investigator will ultimately make a decision that the event is most likely present or absent to the best of his/her ability, blinded to study intervention treatment assignment.

Symptomatic Deep Vein Thrombosis (DVT)

Displaying signs or symptoms of proximal or distal lower extremity DVT, upper extremity DVT, or other DVT based on 1 or more of the following diagnostic criteria:

a. a non-compressible venous segment on compression ultrasonography, or in participants with a history of previous DVT, either a new non-compressible venous segment or a substantial increase (4 mm or more) in the diameter of the vein during full compression in a previously abnormal segment on ultrasonography, or

b. the presence of an intraluminal filling defect on venography, or

c. imaging evidence of cerebral vein or sinus thrombosis, or

d. imaging evidence of other DVT (eg mesenteric vein, renal vein, inferior vena cava, superior vena cava, jugular vein), or

e. DVT documented at autopsy.

Participants with a history of previous DVT or incomplete documentation of the previous episode is available, additional criteria may be integrated with the current event, such as: ultrasonography appearance of the thrombus, or D-dimer at presentation. Soleal or muscular branch DVTs, lower extremity superficial DVT will not be included. The totality of available clinical, imaging and laboratory findings should be considered.

Symptomatic PE

Displaying signs or symptoms suggestive of PE and based on 1 or more of the following diagnostic criteria. (Note: as COVID-19 may also be associated with in situ pulmonary arterial thrombosis, evidence of such associated with symptoms of PE or with deterioration of oxygenation will be considered a symptomatic PE):

a. an intraluminal filling defect on computed tomography (CT) angiography or spiral CT, or

b. an intraluminal filling defect on pulmonary angiography or cutoff of a vessel more than 2.5 mm in diameter, or

c. a perfusion lung scan defect of at least 75% of a segment with corresponding normal ventilation (high probability ventilation-perfusion ([V-Q]) scan), or

d. a non-high probability V-Q scan abnormality associated with DVT documented by ultrasonography or venography, or

e. in the absence of imaging test in a hemodynamically unstable participant, evidence of right ventricular dysfunction by transthoracic or trans esophageal echocardiogram (ESC criteria), or

f. CT or other imaging evidence of in situ thrombosis in one or more pulmonary arterial branches, or

f. PE or in situ pulmonary arterial thrombosis documented at autopsy.

The anatomic extent of PE will be classified as either segmental or greater, or subsegmental. The totality of available clinical, imaging and laboratory findings should be considered.

Myocardial Infarction

The definition of MI is based on the evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia, conforming to the reporting conventions proposed in the Fourth universal definition of MI (Thygesen 2018).

Under these conditions any 1 of the following criteria meets the diagnosis for MI. In addition to the overall adjudication of MI, the subtypes below will also be reported:

- Type 1, spontaneous: Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin [cTn]) with at least 1 value above the 99th percentile of the upper reference limit (URL) and with at least 1 of the following:
    - Symptoms of acute myocardial ischemia
    - New or presumed new, significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB)
    - Development of pathological Q waves in the electrocardiogram (ECG)
    - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology
    - Identification of an intracoronary thrombus by angiography or autopsy
- Type 2, ischemic imbalance: Detection of a rise and/or fall of cardiac biomarker values (preferably [cTn]) with at least 1 value above the 99th percentile of the URL and evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute coronary atherothrombosis, requiring at least 1 of the following:
    - Symptoms of acute myocardial ischemia
    - New or presumed new, significant ST–T changes or new LBBB
    - Development of pathological Q waves in the ECG
    - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology
- Type 3: Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or ventricular fibrillation, but death occurred before cardiac biomarkers were obtained or before cardiac biomarker values would be increased, or MI is detected by autopsy examination.

- Type 4a: Percutaneous coronary intervention (PCI) related MI is defined as MI associated with, and occurring within 48 hours of PCI, with elevation of cardiac biomarker levels (>5 x 99th percentile URL) in participants with normal baseline values (≤99th percentile URL); or a rise of cardiac biomarker levels values >20% if the baseline values are elevated and are stable or falling as long as the absolute post-procedure value is still >5 x 99th percentile URL. In addition, at least 1 of the following:
    - New ischemic ECG changes or new LBBB
    - Development of new pathologic Q waves (Isolated development of new pathological Q waves meets the Type 4a MI criteria if cTn values are elevated and rising but less than 5 x the 99th percentile URL)
    - Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or a side branch occlusion/thrombus, disruption of collateral flow, or distal embolization
    - Post-mortem demonstration of a procedure-related thrombus in the culprit artery, or a macroscopically large circumscribed area of necrosis with or without intra-myocardial hemorrhage
- Type 4b: Stent thrombosis-associated with MI when detected by coronary angiography or autopsy in the setting of acute myocardial ischemia (as in Type 1 MI) and with a rise and/or fall of cardiac biomarker values with at least 1 value above the 99th percentile URL.
- Type 4c: Stent restenosis-associated MI, as detected by coronary angiography or at autopsy, occurring >48 hours after PCI, without evidence of stent thrombosis but with symptoms suggestive of myocardial ischemia, and with elevation of cardiac biomarker values with at least one value above the 99th percentile URL. The following criteria are also required:
    - Does not meet criteria for any other classification of MI
    - Presence of a ≥50% stenosis at the site of previous successful stent PCI or a complex lesion and no other obstructive CAD of greater severity following either initially successful stent deployment, or dilation of a coronary artery stenosis with balloon angioplasty to <50% stenosis.
- Type 5: Coronary artery bypass grafting- (CABG-)-related MI is defined as MI associated with, and occurring within 48 hours of PCI, with elevation of cardiac biomarker levels (>10 x 99th percentile URL) in participants with normal baseline values (≤99th percentile URL); or a rise of cardiac biomarker levels values >20% if the baseline values are elevated and are stable or falling as long as the absolute post-procedure value is still >10 x 99th percentile URL. In addition, at least one of the following:
    - Development of new pathologic Q waves (isolated development of new pathological Q waves meets the Type 5 MI criteria if cTn values are elevated and rising but less than 10 times the 99th percentile URL)
    - Angiographic documented new graft occlusion or new native coronary artery occlusion
    - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology.

Reviewers should also consider possible alternative causes of elevated cardiac biomarkers of necrosis (eg, myocarditis, heart failure, hypertensive crisis, PE, renal failure, sepsis).

Acute Myocardial Infarction, Spontaneous Reinfarction

- For participants with no recent revascularization in whom biomarkers from a recent MI remain elevated, Criteria 1 and 2 must be met:
  - Cardiac biomarker re-elevation defined as:
    - Greater than the 99th percentile of the URL; and
    - Increase by ≥20% of the previous value; and
    - Documentation that the biomarker assayed was decreasing prior to the suspected new MI

AND

  - At least 1 of the following additional supportive criteria:
    - Ischemic discomfort at rest lasting ≥10 minutes; or
    - New ECG changes (distinct from the first MI) meeting the criteria outlined above;
- Within 48 hours after PCI a participant must have
  - Cardiac biomarker >3× the 99th percentile of the URL and, if the pre-PCI biomarker was >99th percentile of the URL, both an increase by ≥20% over the previous value and documentation that the biomarker was decreasing prior to the event.

Note: symptoms are not required.

- Within 72 hours after CABG a participant must have BOTH:
  - Cardiac biomarker >5× the 99th percentile of the URL and, if the pre-CABG biomarker was >99th percentile of the URL, both an increase by at least ≥20% over the previous value and documentation that the biomarker was decreasing prior to the event.

AND

  - At least 1 of the following supportive criteria:
    - Development of new, abnormal Q waves (>30 msec in duration and ≥0.1 mV in depth) in ≥2 contiguous leads, or new abnormal R waves (≥30 msec in duration and > depth of the S wave) in V1 and V2 consistent with posterior infarction, or new LBBB, OR
    - Angiographically documented new graft or native coronary occlusion, OR
    - Imaging evidence of new loss of viable myocardium.

Note: symptoms are not required.

Note: For periprocedural MIs, CK-MB remains the preferred biomarker given the greater experience. However, if cardiac troponin measurements are the only cardiac biomarker data available, they may be used by the CEC, along with the ECG and clinical scenario, in the adjudication of suspected MI after revascularization.

Ischemic Stroke

An acute episode of neurological dysfunction caused by focal or global brain vascular injury and includes all strokes that are not of a primary hemorrhagic etiology. This includes fatal and nonfatal strokes. Any sudden onset of a neurologic deficit that last for more than 24 hours will be consider a stroke. If it is determined that a stroke has occurred, it will be further categorized into 1) ischemic stroke, 2) hemorrhagic stroke and 3) undetermined stroke as defined below.

Ischemic Stroke

- Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of CNS tissue. Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

Hemorrhagic Stroke

- Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.

Undetermined Stroke

- Undetermined stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as ischemic or hemorrhagic stroke.

Acute Limb Ischemia

Acute ischemia in the limb caused by arterial emboli, arterial thrombosis, or arterial trauma from a vascular procedure with

- Clinical history suggesting a rapid or sudden decrease in limb perfusion, and either of the following below:
- New pulse deficit with associated rest pain, pallor, paresthesia, or paralysis,

OR

Confirmation of arterial obstruction by imaging (including ultrasound, CT, magnetic resonance imaging, or conventional angiography), surgical findings, or pathology

Non-CNS Systemic Embolization

Non-CNS systemic embolism is defined as abrupt vascular insufficiency associated with clinical or radiological evidence of arterial occlusion in the absence of other likely mechanisms, (eg, trauma, atherosclerosis, instrumentation). In the presence of atherosclerotic peripheral vascular disease, diagnosis of embolism to the lower extremities should be made with caution and requires angiographic demonstration of abrupt arterial occlusion.

Because COVID-19 participants may develop in situ thrombosis or arterial thromboembolism that may be difficult to differentiate, for the purposes of this protocol, any documented arterial obstruction of blood flow to an internal organ (eg kidney, small intestine, large intestine) or to an extremity will be considered a non-CNS systemic embolization.

Deaths

The primary cause of death will be documented based on the example categories summarized below. Deaths will also be documented to be either related to COVID-19 or not related to COVID-19.

Because some COVID-19-related causes of death may be attributable to cardiovascular causes (eg, MI) and some may be attributable to non-cardiovascular causes (eg, respiratory failure, viral pneumonia), subsequent categorizations of the cause of death may be defined in summary analyses based on details provided in the SAP.

Death Causes

- Cardiac arrest due to respiratory failure
- MI
- Ischemic stroke
- Intracranial hemorrhage
- Congestive heart failure
- Coronary heart disease
- Cardiogenic shock
- PE
- Atherosclerotic vascular disease
- Sudden or unwitnessed death
- Hemorrhage, not intracranial
- Other cardiovascular
- Accidental / trauma
- Respiratory failure, viral pneumonia
- Respiratory failure
- Infection
- Malignancy
- Suicide
- Liver failure
- Renal failure

- Sepsis
- Hemorrhage, not intracranial
- Other noncardiovascular

Sudden death would include any death in which there is an abrupt collapse of the respiratory and cardiovascular systems and death occurs during which time no other evaluations are performed either with ECG monitoring, imaging, or other laboratory testing.

Unwitnessed death is a death where the subject is discovered dead after last having been seen in a stable state. An unwitnessed death would not include death from a chronic, deteriorating noncardiovascular illness such as cancer.

Unknown Cause

If no information is available regarding the cause of death other than an oral communication from a relative, friend, or authorized representative without any information regarding the immediate cause, the primary investigator/investigative study staff will classify the cause of death as unknown.

The primary investigator/investigative study staff should record all efforts made to obtain information of the cause of death in the source documents.

Acute Renal Failure

Acute renal failure will be diagnosed if either of the following criteria are satisfied:

- Dialysis is administered (Note: participants already on dialysis at screening are excluded from study participation)
- Two consecutive eGFR of <15 mL/min/1.73m^2 are observed occurring greater than 24 hours apart

COVID Digit

COVID digit will be defined as new onset and unexplained manifestations of pain, burning, swelling or discoloration of the fingers and toes and unlikely to be attributable to other causes (eg, insect bite, allergic reaction) (Landa 2020).

Acute Respiratory Distress Syndrome (ARDS)

Acute Respiratory Distress Syndrome is defined as a type of acute diffuse, inflammatory lung injury, leading to increased pulmonary vascular permeability, increased lung weight, and loss of aerated lung tissue. The clinical hallmarks are hypoxemia and bilateral radiographic opacities, associated with increased venous admixture, increased physiological dead space, and decreased lung compliance. The morphological hallmark of the acute phase is diffuse alveolar damage (ie, edema, inflammation, hyaline membrane, or hemorrhage).

The Berlin definition of ARDS include the following criteria (ARDS 2012):

- Timing: within 1 week of a known clinical insult or new or worsening respiratory symptoms
- Chest imaging (chest radiograph or computed tomography scan): bilateral opacities – not fully explained by effusions, lobar/lung collapse, or nodules
- Origin of edema: respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present.
- Oxygenation (if altitude is higher than 1,000 m, the correction factor should be calculated as follows: [PaO2/FIO2 x (barometric pressure/760)]):
  - Mild: 200 mm Hg $<PaO_2/FIO_2 \leq 300$ mm Hg with PEEP or CPAP ≥ 5 cm H_2O
  - Moderate: 100 mm Hg $<PaO_2/FIO_2 \leq 200$ mm Hg with PEEP ≥ 5 cm H_2O
  - Severe: $PaO_2/FIO_2 \leq 100$ mm Hg with PEEP ≥ 5 cm H_2O

10.4. Appendix 4: Nonmajor Clinically Relevant Bleeding Event Criteria

Nonmajor clinically relevant bleeding is defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study intervention treatment, or associated with discomfort for the subject such as pain or impairment of activities of daily life.

Examples of nonmajor clinically relevant bleeding are:

- Epistaxis if it lasts for more than 5 minutes, if it is repetitive (ie, 2 or more episodes of true bleeding, ie, not spots on a handkerchief, within 24 hours), or leads to an intervention (packing, electrocautery)
- Gingival bleeding if it occurs spontaneously (ie, unrelated to tooth brushing or eating), or if it lasts for more than 5 minutes
- Hematuria if it is macroscopic, and either spontaneous or lasts for more than 24 hours after instrumentation (eg, catheter placement or surgery) of the urogenital tract
- Macroscopic gastrointestinal hemorrhage: at least 1 episode of melena or hematemesis, if clinically apparent
- Rectal blood loss, if more than a few spots
- Hemoptysis, if more than a few speckles in the sputum
- Intramuscular hematoma
- Subcutaneous hematoma if the size is larger than 25 cm^2 or larger than 100 cm^2 if provoked
- Multiple-source bleeding

10.5. Appendix 5: Regulatory, Ethical, and Study Oversight Considerations

10.5.1. Regulatory and Ethical Considerations

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study intervention to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator.
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, eConsent, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable.
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable.
- Documentation of investigator qualifications (eg, curriculum vitae).
- Completed investigator financial disclosure form from the principal investigator, where required.
- Signed and dated clinical trial agreement, which includes the financial agreement.
- Any other documentation required by local regulations.

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved eConsent (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials

- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the eConsent, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to eConsent and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study intervention
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable eConsent revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1, Study-Specific Ethical Design Considerations.

10.5.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

10.5.3. Informed Consent (Remote eConsent) Process

Each participant (or a legally acceptable representative) must give remote eConsent according to local requirements after the nature of the study has been fully explained. The remote e-consent must be electronically signed before performance of any study-related activity. The remote e-consent(s) that is/are used must be approved by both the sponsor and by the reviewing IRB and be in a language that the participant can read and understand. The remote e-consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy. After having obtained the consent, a copy of the remote e-consent must be sent to the participant.

Before enrollment in the study, the investigator or an authorized member of the study personnel must explain to potential participants or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive. Participants will be told that refusal to take part in the study will not prejudice future treatment. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow-up if needed and that their records may be accessed by HAs and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By electronically signing the remote eConsent, the participant or legally acceptable representative is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The participant or legally acceptable representative will be given sufficient time to read the eConsent and the opportunity to ask questions via phone, Interactive Web Interface and/or in-person visit. Once the participant or legally acceptable representative understands all aspects of the remote eConsent, consent should be appropriately recorded by means of the participant's or legally acceptable representative's personally dated signature via electronic signature. After having obtained the consent, the participant will receive a copy of the remote eConsent for their records.

Sites will use an electronic system to obtain informed consent instead of a paper process as allowed by local regulations and IRB. The ability for participants or their legally acceptable representatives to review the paper informed consent form is always an option at sites utilizing electronic informed consent. Overall the consent/assent process will remain the same, as described in this section.

A participant who is rescreened is not required to sign another eConsent if the rescreening occurs within 14 days from the previous eConsent signature date.

If the participant [or legally acceptable representative] is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the eConsent after the oral consent of the participant [or legally acceptable representative] is obtained.

10.5.4. Data Protection

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant (or his or her legally acceptable representative) includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

10.5.5. Committees Structure

Independent Data Monitoring Committee

An 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. The IDMC will include, but is not limited to, a clinical chairman, physician(s) experienced in clinical studies, but not participating in this study, and at least 1 statistician. Details of the composition, roles, responsibilities, and processes of the IDMC will be documented in its charter. The IDMC will review results of the planned IA and make a recommendation whether the study should be continued as planned, modified, or terminated prematurely due to futility or safety.

Executive Committee

The Executive Committee (EC) consists of members of the academic leadership of the study and from the sponsor. Ad hoc members may be appointed as necessary. The EC has overall responsibility for the design, conduct and reporting of the study. The EC will monitor overall safety during the study and will receive any recommendations from the IDMC regarding possible additional analyses or modifications to the study and decide whether to accept them. The EC will oversee the implementation of any modifications to the study and publication of the results.

10.5.6. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding rivaroxaban or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of rivaroxaban, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study-site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law. The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

10.5.7. Data Quality Assurance

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites and review of protocol procedures with the investigator and study personnel before the study.

Guidelines for eCRF completion will be provided and reviewed with participating study personnel before the start of the study. The sponsor will review eCRF data for accuracy and completeness via centralized, remote, and/or on-site monitoring methods; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

10.5.8. Case Report Form Completion

Electronic case report forms are prepared and provided by the sponsor for each participant. All data relating to the study that is not collected directly from the EMR into the eDC tool must be recorded in eCRF. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

Specified study data will be transcribed by study personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the participant's source documents. Data must be entered into eCRF in English. The eCRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

All participative measurements (eg, symptom assessment or other questionnaires) should be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to a eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study personnel.

10.5.9. Source Documents

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data will be recorded directly into the eCRF and will be considered source data (if the data is not captured from EMR):

- Race

- Height and weight
- Smoking status (current or past smoker)
- Assessment of Symptoms

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

Appendix 1 Referral letter from treating physician, or

Appendix 2 Complete history of medical notes at the site, or

Appendix 3 Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the eCRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the eCRF.

10.5.10. Monitoring

The sponsor will use a combination of monitoring techniques (central, remote, and/or on-site monitoring) to monitor this study. Due to the ongoing pandemic, on-site monitoring visits may not take place. For any remote contacts, it is expected that study personnel will be available to provide an update on the progress of the study at the site. Central monitoring will take place for data identified by the sponsor as requiring central review.

10.5.11. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

10.5.12. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

10.5.13. Study and Site Start and Closure

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the study start date.

Study/Site Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local HAs, the sponsor's procedures, or GCP guidelines

- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.6. Appendix 6: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.6.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the intervention. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per ICH)

Note: The sponsor collects adverse events starting with the signing of the eConsent (refer to All Adverse Events under Section 8.3.1, Time Period for Collecting Adverse Event and Serious Adverse Event Information, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and European Union Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening
  (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

For the purposes of this study, efficacy and safety outcomes (including all bleeding events) will not be considered as adverse events or serious adverse events.

Serious Adverse Events Confirmed as Study Endpoints

Study endpoint events (ie, symptomatic DVT, PE, MI, ischemic stroke, acute limb ischemia, non-CNS systemic embolization, hospitalizations, all-cause death, and major, critical site and fatal bleeding, and nonmajor clinically relevant bleeding) and non-endpoint bleeding will undergo

verification/adjudication by qualified study investigators. To protect the integrity of the study, events that are confirmed to be endpoints will not be unblinded or reported to either HAs or investigators as safety reports unless otherwise requested by HAs or Ethics Committees. After study completion, these events will be included in the final analysis which will be unblinded and submitted to HAs with the study report.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For rivaroxaban, the expectedness of an adverse event will be determined by whether or not it is listed in the IB.

10.6.2. Attribution Definitions

Assessment of Causality

The causal relationship to study intervention is determined by the investigator. The following selection should be used to assess all adverse events.

Related

There is a reasonable causal relationship between study intervention administration and the adverse event.

Not Related

There is not a reasonable causal relationship between study intervention administration and the adverse event.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

10.6.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

10.6.4. Procedures

All Adverse Events

Adverse events must be recorded using medical terminology in the EMR and/or eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the EMR and/or eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

Serious Adverse Events

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon the participant's discontinuation from the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition (refer to Adverse Event Definitions and Classifications in Appendix 6, Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).

Information regarding serious adverse events will be transmitted to the sponsor using a serious adverse event reporting form and safety report form of the eCRF, which must be completed and reviewed by a physician from the study site and transmitted in a secure manner to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be transmitted in a secure manner electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

10.6.5. Product Quality Complaint Handling

Definition

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality,

durability, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

Procedures

All initial PQCs must be reported to the sponsor by the study personnel within 24 hours after being made aware of the event.

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

10.6.6. Contacting Sponsor Regarding Safety, Including Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues, PQC, or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

10.7. Appendix 7: Contraceptive and Barrier Guidance

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.2, Pregnancy and Appendix 6, Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. If there is a question about menopausal status in women on HRT, the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently sterile (for the purpose of this study)**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system
• Bilateral tubal occlusion
• Azoospermic partner *(vasectomized or due to medical cause)* *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] – oral – injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male or female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)

a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.
b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention.
c) Male condom and female condom should not be used together (due to risk of failure with friction).

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INVESTIGATOR AGREEMENT

JNJ-39039039; BAY 59-7939 (rivaroxaban) Clinical Protocol 39039039DVT3004

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): _____

Institution: Janssen Research & Development

Signature: PPD PPD Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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Status: Approved, Date: 04 June 2020