Janssen Research & Development *

Clinical Protocol

Medically Ill Patient **A**ssessment of **R**ivaroxaban Versus Placebo **IN** Reducing Post-Discharge Venous Thrombo-**E**mbolism **R**isk (**MARINER**)

Protocol RIVAROXDVT3002; Phase 3 BAY 59-7939/17261

Amendment INT-7

JNJ-39039039; BAY 59-7939 (rivaroxaban)

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This compound is approved for marketing in 6 indications.

This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

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

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	27 January 2014
Amendment INT-7	31 March 2017
Amendment INT-6	19 June 2015
Amendment INT-5	15 June 2015
Amendment INT-4	19 January 2015
Amendment INT-3	8 December 2014
Amendment INT-2	11 April 2014
Amendment INT-1	14 March 2014

Amendments are listed beginning with the most recent amendment.

Amendment INT-7 (31 March 2017)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment is that because this is an event-driven study, additional subjects will need to be enrolled to allow for more primary efficacy outcome events to accumulate, due to a lower than expected blinded pooled event rate.

Applicable Section(s)	Description of Change(s)

Rationale: The upper limit for the number of randomized subjects was increased to allow for the accumulation of more primary efficacy outcome events.

Applicable Section(s)	Description of Change(s)
Synopsis Overview of Study Design; Synopsis Sample Size Determination; 3.1. Overview of Study Design; 11.2.Sample Size Determination	The total number of subjects that may be randomized was increased from approximately 9,000 to approximately 12,000 subjects.

Rationale: Revisions were made to align the timing of the interim analysis to when approximately 50% of the total anticipated subjects with observed blinded pooled primary efficacy outcome events at the end of the study will be obtained.

Applicable Section(s)	Description of Change(s)
Synopsis Overview of Study Design; Synopsis Interim Analysis; 3.1. Overview of Study Design; 11.7. Interim Analysis	The timing of the interim analysis was changed from having observed adjudicated primary efficacy outcome events in approximately 80 subjects to approximately 50% of subjects based on the expected total number of events. Consequently, 'targeted' in 'targeted total number of events' was changed to 'expected total number of events' based on the actual observed blinded pooled event rate because this event rate is lower than the assumed rate.

Rationale: Changes were made to clarify the term of 'major protocol deviations' in the per-protocol analysis set.	
11.1.1. Analysis Sets	The term 'major' in 'major protocol deviations' was changed to 'key' protocol deviations, because 'key' accurately reflects that only a subset of major deviations will be excluded from the per-protocol analysis set.
Rationale: Minor errors were noted.	
Applicable Section(s)	Description of Change(s)
Throughout the protocol 3.1. Overview of Study Design	Minor grammatical, formatting or spelling changes were made. For consistency with the rest of the document, the principal safety outcome was added.

Amendment INT-6 (19 June 2015)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reasons for the amendment are to clarify prescribed thromboprophylaxis during index hospitalization and capping during enrollment.

Applicable Section(s)	Description of Change(s)
Rationale: Prescribed thromboprophylaxis has been clarified.	
Applicable Section(s)	Description of Change(s)
4. SUBJECT POPULATION, Section 4.1 Inclusion Criteria.	Inclusion Criterion # 4. Prescribed maximum daily dose of thromboprophylactic agents allowed was clarified.
Section 5. Treatment Allocation and Blinding	Capping for subgroups during enrollment and related communication with sites were clarified.

Please note that description of changes for INT-1 to INT-5 can be found in Attachment 5.

SYNOPSIS

Medically Ill Patient **A**ssessment of **R**ivaroxaban Versus Placebo **IN** Reducing Post-Discharge Venous Thrombo-**E**mbolism **R**isk (**MARINER)**

DESCRIPTION OF THE COMPOUND

Rivaroxaban is an oral, direct acting, Factor Xa (FXa) inhibitor anticoagulant that has been under development for the treatment of several thrombosis-mediated conditions. Rivaroxaban is marketed under the trade name XARELTO® and has been approved for multiple indications worldwide. The clinical development program for rivaroxaban is extensive. Over 70,000 subjects have been studied from Phase 1 through multiple large Phase 4 studies as of 15 March 2014, covering several indications and potential indications in the overall clinical development program. Over 40,000 of these subjects have been exposed to rivaroxaban in completed and ongoing company-sponsored interventional clinical trials and non-interventional studies, with the total daily doses of rivaroxaban ranging between 5 mg and 60 mg.

For the most comprehensive nonclinical and clinical information regarding the efficacy and safety of rivaroxaban, refer to the latest version of the Investigator's Brochure [19].

OBJECTIVE AND HYPOTHESIS

Primary Objective

The primary objective is to assess the efficacy and safety of rivaroxaban compared with placebo in the prevention of symptomatic venous thromboembolism (VTE: lower extremity deep vein thrombosis [DVT] and non-fatal pulmonary embolism [PE]) and VTE-related death (death due to PE or death in which PE cannot be ruled out as the cause) post-hospital discharge in high-risk, medically ill patients.

Secondary Objectives

The secondary objectives are to compare rivaroxaban with placebo in the following post-hospital discharge outcomes in high-risk, medically ill patients:

- VTE-related death (death due to PE or death in which PE cannot be ruled out as the cause)
- Symptomatic VTE (lower extremity DVT and non-fatal PE)
- The composite of symptomatic VTE (lower extremity DVT and non-fatal PE) and all-cause mortality (ACM)
- The composite of symptomatic VTE (lower extremity DVT and non-fatal PE), myocardial infarction (MI), non-hemorrhagic stroke and cardiovascular (CV) death (death due to a known CV cause and death in which a CV cause cannot be ruled out; by this definition, a VTE-related death is considered a CV death)
- ACM

Exploratory Objectives

The exploratory objectives are to compare rivaroxaban with placebo, in the following post-hospital discharge outcomes in high-risk, medically ill patients:

- Symptomatic lower extremity DVT
- Symptomatic non-fatal PE
- Symptomatic upper extremity DVT
- MI
- Non-hemorrhagic stroke
- Re-hospitalization for symptomatic VTE (lower extremity DVT and non-fatal PE) within 30 days after randomization

Pharmacokinetic Objective

The pharmacokinetic (PK) objective is to assess the kinetics of rivaroxaban in high-risk, medically ill patients, and to describe drug exposure based on creatinine clearance (CrCl).

Medical Resource Utilization and Health Economics Objective

The medical resource utilization and health economics objective is to assess the following cost drivers, ie, re-hospitalization (including emergency room [ER] visits, intensive care unit and cardiac care unit stays), length of stay and subject discharge destination (after re-hospitalization).

Safety Objectives

The safety objectives are to compare rivaroxaban with placebo in the following bleeding outcomes in high-risk, medically ill patients:

- Major bleeding using validated International Society on Thrombosis and Haemostasis (ISTH) bleeding criteria.
- Non-major clinically relevant bleeding
- Other bleeding

Overall safety will also be assessed.

Hypotheses

The primary hypothesis is that rivaroxaban is superior to placebo in the prevention of the composite of symptomatic VTE (lower extremity DVT and non-fatal PE) and VTE-related death (death due to PE or death in which PE cannot be ruled out as the cause). The secondary hypotheses are that rivaroxaban is superior to placebo in the prevention of 1) VTE-related death (death due to PE or death in which PE cannot be ruled out as the cause), 2) symptomatic VTE (lower extremity DVT and non-fatal PE), 3) the composite of symptomatic VTE (lower extremity DVT and non-fatal PE) and ACM, 4) the composite of symptomatic VTE (lower extremity DVT and non-fatal PE), MI, non-hemorrhagic stroke and CV death (death due to a known CV cause and death in which a CV cause cannot be ruled out; by this definition, a VTE-related death is considered a CV death) and 5) ACM alone.

OVERVIEW OF STUDY DESIGN

This is a multicenter, prospective, randomized, double-blind, placebo-controlled, event-driven study designed to evaluate rivaroxaban, compared with placebo, in the prevention of symptomatic VTE (lower extremity DVT and non-fatal PE) events and VTE-related deaths (death due to PE or death in which PE cannot be ruled out as the cause) for a period of 45 days post-hospital discharge. The study consists of a screening phase, a 45-day double-blind treatment phase, and a 30-day safety follow-up period.

The subject population comprises men and women aged 40 years and older who have completed screening no later than 1 day after leaving the hospital and who have been hospitalized for the new onset or exacerbation of 1 of the following medical conditions:

- Heart Failure (HF) with a reduced left ventricular ejection fraction (LVEF ≤45%)
- Acute respiratory insufficiency or acute exacerbation of chronic obstructive pulmonary disease (COPD)
- Acute ischemic stroke (including spinal cord infarction if no evidence of intramedullary, subdural or epidural hemorrhage)
- Acute infectious disease
- Inflammatory disease, including rheumatic disease

The index hospitalization must be at least 3 and no more than 10 consecutive days in duration. In order to be eligible, subjects must have an increased VTE risk, as demonstrated by a total modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) VTE Risk Score of:

- ≥4, or
- 3 with D-dimer > 2XULN, or
- 2 with D-dimer > 2XULN

In addition, subjects must have received treatment during the index hospitalization with LMWH or UFH.

Any patient with a medical condition that will require use of any parenteral or oral anticoagulation (eg, atrial fibrillation) during the study is not eligible for participation. In addition, patients at particularly increased risk of bleeding and those using medications that might interact with the study drug will be excluded.

Subjects who meet all of the inclusion and none of the exclusion criteria will be randomly assigned to receive rivaroxaban or placebo. Randomization should occur on the same day as or the day after the subject leaves the hospital, and may occur at the hospital, clinic or other discharge destination. Subjects will be randomized by strata including creatinine clearance and country.

After randomization, subjects will receive double-blind treatment with rivaroxaban 10 mg (7.5 mg for subjects with a CrCl ≥30 mL/min and <50 mL/min) daily or matching placebo daily. Placebo has been chosen as the comparator because of current guidelines which recommend against thromboprophylaxis in medically ill patients after hospital discharge. The first dose of study drug should be administered no later than the day after the subject leaves the hospital and as soon after randomization as possible. Subjects will be instructed to discontinue study drug after they take a dose on Day 45, and complete an end of treatment visit within the next 4 days. ***Regardless of the day on which the Day 45 Visit occurs, no study drug may be taken after Day 45.*** The subject must be assessed 30 days later for safety follow-up. This will be the last contact with the subject unless extended follow-up for safety is required.

If a subject has a suspected efficacy or bleeding outcome event during the study, the treating physician should exercise clinical judgment and follow established guidelines to apply the standard of care. Unblinding of study drug should not be necessary. Anticoagulation regimens do not require adjustment regardless of treatment group assigned when study drug is administered in the doses used in this study. There is no specific reversal agent for rivaroxaban; management of the subject with a bleeding event should not be impacted by knowledge of study drug treatment.

Rivaroxaban will not be provided to subjects after they complete study treatment, unless required by local regulations. Randomization in this study is preceded by a hospitalization for an acute illness and the study drug treatment phase extends for 45 days after randomization to correspond to the period of greatest risk

for VTE. Chronic therapy with the study drug is not being tested. It will only be after data from the entire study is analyzed that the sponsor can determine if the population at risk will benefit from treatment.

The primary efficacy outcome is the composite of all symptomatic VTE events (lower extremity DVT and non-fatal PE) and VTE-related death (death due to PE or death in which PE cannot be ruled out as the cause), from randomization up to Day 45. The targeted total number of primary efficacy outcomes in this event-driven study is 161. It is estimated that a total of approximately 8,000 subjects will need to be randomized to either rivaroxaban or placebo in a 1:1 ratio. In the event that the actual observed blinded pooled event rate is lower than the assumed rate, more subjects may be enrolled to accumulate additional outcome events. Randomization in this study may be stopped at approximately 12,000 subjects for administrative considerations even if the targeted 161 events have not been observed by then. An interim analysis for futility will be conducted when approximately 50% of subjects with adjudicated primary efficacy outcome events have been observed (about 50% of the expected total number of events based on the actual observed blinded pooled event rate even if this event rate is lower than the assumed rate). The principal safety outcome for this study is ISTH major bleeding.

For population PK analyses, based on the model performance and the high variability of the PK parameters observed in the MAGELLaN study, 2 blood samples (at pre-dose and 1-4 hours after study drug administration) will be collected at the Day 7 visit and 2 blood samples (at 3 to 7 and 7 to 12 hours after study drug administration) will be collected at the Day 21 visit for each subject for up to 600 subjects (300 rivaroxaban subjects [200 subjects in the 10 mg daily group and 100 subjects in the 7.5 mg daily group] and 300 in the placebo group). The sparse blood samples for PK analyses will be collected in selected sites only.

An Executive Committee (EC), an Independent Data Monitoring Committee (IDMC) and a Clinical Event Committee (CEC) will be commissioned for this study. All committees will be governed by separate charters, see Section 3.3.

SUBJECT POPULATION

The subject population comprises men and women age 40 years and older who have completed screening no later than 1 day after leaving the hospital and who have been hospitalized for the new onset or exacerbation of 1 of the following medical conditions:

- HF with a reduced LVEF (LVEF ≤ 45%)
- Acute respiratory insufficiency or acute exacerbation of COPD
- Acute ischemic stroke (including spinal cord infarction if no evidence of intramedullary, subdural or epidural hemorrhage)
- Acute infectious disease
- Inflammatory disease, including rheumatic disease

The index hospitalization must be at least 3 and no more than 10 consecutive days in duration. In order to be eligible, subjects must have an increased VTE risk, as demonstrated by a total modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) VTE Risk Score of:

- ≥4, or
- 3 with D-dimer > 2XULN, or
- 2 with D-dimer > 2XULN

In addition, subjects must have received treatment during the index hospitalization with low molecular weight heparin (LMWH) or unfractionated heparin (UFH).

Any patient with a medical condition that will require use of any parenteral or oral anticoagulation (eg, atrial fibrillation, other medical condition) during the study is not eligible for participation. In addition, patients at particularly increased risk of bleeding and those using medications that interact with the study drug will be excluded.

DOSAGE AND ADMINISTRATION

Treatment groups in this study are rivaroxaban and placebo. Subjects will be randomly assigned in a 1:1 ratio to receive rivaroxaban 10 mg daily (or 7.5mg daily in subjects with CrCl ≥30 mL/min and <50 mL/min) or matching placebo daily. Randomization will be stratified by subjects with CrCl ≥30 mL/min and <50 mL/min versus subjects with CrCl ≥50 mL/min and by country.

The first dose of study drug should be administered no later than the day after the subject leaves the hospital and as soon after randomization as possible. The date and time of the first dose of study drug and the last dose of LMWH or UFH should be recorded as accurately as possible. The first dose of study drug should not be delayed to allow administration under supervision. All subjects should take study drug (rivaroxaban or placebo) daily with or without food at approximately the same time each day, and discontinue study drug after they take a dose on Day 45. ***Regardless of the day on which the Day 45 Visit occurs, no study drug may be taken after Day 45***.

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.

Interruption of Study Drug

Study drug may be interrupted temporarily as necessary for invasive procedures or as medically needed (eg, in the setting of a bleeding event or a required prohibited therapy). If a subject is hospitalized for any reason other than a VTE-related event or bleeding, study drug should be continued during hospitalization unless the treating physician feels that anticoagulation is clinically warranted. Subjects may be placed on appropriate anticoagulation at the discretion of the treating physician. In that case, study drug needs to be temporarily interrupted and can be restarted upon discharge at the discretion of the investigator. These interruptions will be recorded on the electronic case report form (eCRF).

During the study, should the subject develop any condition, which in the investigator's judgment requires long-term anticoagulation thromboprophylaxis, or fibrinolysis, the subject will have study treatment either temporarily interrupted or permanently discontinued and will be managed as deemed appropriate by the treating physician. The subject will be asked to continue in the study to be followed for efficacy and safety outcomes.

EFFICACY EVALUATIONS/OUTCOMES

- The primary efficacy outcome is the composite of all symptomatic VTE events (lower extremity DVT and non-fatal PE) and VTE-related death (death due to PE or death in which PE cannot be ruled out as the cause)
- The secondary efficacy outcomes are the following:
  - VTE-related death (death due to PE or death in which PE cannot be ruled out as the cause)
  - Symptomatic VTE (lower extremity DVT and non-fatal PE)
  - The composite of symptomatic VTE (lower extremity DVT and non-fatal PE) and ACM
  - The composite of symptomatic VTE (lower extremity DVT and non-fatal PE), MI, non-hemorrhagic stroke and CV death (death due to a known CV cause and death in which a CV cause cannot be ruled out; by this definition, a VTE-related death is considered a CV death)
  - ACM

- Exploratory efficacy outcomes are:
  - Symptomatic lower extremity DVT
  - Symptomatic non-fatal PE
  - Symptomatic upper extremity DVT
  - MI
  - Non-hemorrhagic stroke
  - Re-hospitalization for symptomatic VTE (lower extremity DVT and non-fatal PE) within 30 days after randomization

Any clinical event that suggests the possibility that an efficacy outcome event has occurred (including acute coronary syndrome (ACS) and transient ischemic attack (TIA) will be sent for adjudication. If a subject has a suspected efficacy outcome event during the study, the treating physician should exercise clinical judgment and follow established guidelines to apply the standard of care. Unblinding of study drug should not be necessary, as anticoagulation regimens do not require adjustment regardless of use of placebo vs rivaroxaban when administered in the doses used in this study.

SAFETY EVALUATIONS/ OUTCOMES

- The principal safety outcome is major bleeding using validated ISTH bleeding criteria.
- Other safety outcomes are non-major clinically relevant bleeding and other bleeding.

Overall safety will also be assessed.

An ISTH major bleeding event is defined as overt bleeding associated with: a fall in hemoglobin of 2 g/dL or more, or leading to a transfusion of 2 or more units of packed red blood cells or whole blood, or bleeding that occurs in a critical site: eg, intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or a fatal outcome (for details on definitions see Section 9.5).

Non-major 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 treatment, or associated with discomfort for the subject such as pain or impairment of activities of daily life.

Other bleeding is defined as any other overt bleeding that does not meet the ISTH criteria for major or non-major clinically relevant bleeding.

Any clinical event that suggests the possibility that a bleeding outcome event has occurred will be sent for adjudication. If a subject has a serious bleeding event during study drug treatment, routine measures should be considered as described in Section 9.5.2. Unblinding of study drug should not be necessary. As there is not a specific reversal agent for rivaroxaban, management of the subject should not be impacted by knowledge of study drug treatment.

STATISTICAL METHODS

Key Analysis Set and Analysis Phase

- Intention-to-Treat (ITT): This analysis set consists of all randomized subjects who have a signed valid informed consent.
- Up-to-Day-45: This analysis phase includes all data from randomization to Day 45 (inclusive).

Sample Size Determination

This is an event-driven study. The targeted total number of primary efficacy outcome events is 161, based on the ITT analysis set and Up-to-Day-45 analysis phase. If a subject has multiple events, only the first is counted towards study size determination.

This targeted total number of events is determined using statistical software East 5.3 based on the primary efficacy analysis (defined later) and the following assumptions:

- 40% relative risk reduction (RRR) in the primary efficacy outcome based on the ITT analysis set and Up-to-Day-45 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 161 events, it is estimated that a total of approximately 8,000 subjects 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 2.5%. In the event that the actual observed blinded pooled event rate is lower than the assumed rate, more subjects may be enrolled to accumulate additional outcome events. Randomization in this study may be stopped at approximately 12,000 subjects for administrative considerations even if the targeted 161 events have not been observed by then. The total number of VTE-related death events may also be taken into account when deciding to stop randomization.

Efficacy Analyses

Primary Efficacy Outcome

The primary efficacy outcome will be analyzed based on time from randomization to the first occurrence of symptomatic VTE (lower extremity DVT and non-fatal PE) and VTE-related death (death due to PE or death in which PE cannot be ruled out as the cause) in the ITT analysis set and Up-to-Day-45 analysis phase. The primary statistical alternative hypothesis is that rivaroxaban is superior to placebo on the primary efficacy outcome.

The primary statistical hypothesis will be tested using Cox proportional hazards model, stratified by subjects with CrCl ≥30 mL/min and <50 mL/min versus subjects with CrCl ≥50 mL/min, with the treatment (as randomized) as the only covariate. This primary efficacy analysis will be based on the ITT analysis set and Up-to-Day-45 analysis phase. Subjects will be analyzed according to the treatment group to which they are randomized, regardless of actual treatment received. As an operational arrangement, the 2-sided p-value will be reported and if it is less than the 2-sided alpha of 0.05, then superiority of the study drug will be declared if the observed survival functions favor rivaroxaban.

The point estimate and corresponding 95% confidence interval (CI) for the HR (rivaroxaban to placebo) will be provided based on the 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 adding a treatment by logarithm-transformed time interaction into the 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, both in HR and direction, will be assessed by subgroups and their interactions with treatment (for details see Section 11.3). Analysis methods will be detailed in the SAP.

Secondary Efficacy Outcomes

Each secondary efficacy outcome will be analyzed based on time from randomization to the first occurrence in the ITT analysis set and the Up-to-Day 45 analysis phase. The same stratified Cox model as that for the primary efficacy outcome will be used. Details will be provided in the SAP.

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 sequentially using a closed testing procedure in the following hierarchical order, each at alpha of 0.05 (2-sided):

- VTE-related death (death due to PE or death in which PE cannot be ruled out as the cause)
- Symptomatic VTE (lower extremity DVT and non-fatal PE)
- The composite of symptomatic VTE (lower extremity DVT and non-fatal PE) and ACM
- The composite of symptomatic VTE (lower extremity DVT and non-fatal PE), MI, non-hemorrhagic stroke and CV death (death due to a known CV cause and death in which a CV cause cannot be ruled out; by this definition, a VTE-related death is considered a CV death)
- ACM

Exploratory Efficacy Outcomes

Each exploratory outcome will be summarized by treatment groups based on the ITT analysis set and Up-to-Day-45 analysis phase.

Pharmacokinetic Analyses

The population PK model will characterize and predict the overall exposure to rivaroxaban and determine different PK parameters.

Medical Resource Utilization and Health Economics

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

Safety Analyses

Bleeding Outcomes

The principal safety outcome will be analyzed based on time from randomization to the first occurrence of ISTH major 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. Subjects will be analyzed according to study drug received. If a subject inadvertently receives both drugs, the subject will be analyzed as randomized. Non-major clinically relevant bleeding will be analyzed based on time from randomization to the first occurrence. The same analysis as that for the principal safety outcome will be used.

Interim Analysis

An interim analysis for futility will be conducted when approximately 50% of subjects with adjudicated primary efficacy outcome events have been observed (about 50% of the expected total number of events based on the actual observed blinded pooled event rate even if this event rate is lower than the assumed rate) and there will be no alpha adjustment to the final analysis (for details see Section 11.7).

Benefit-Risk Analysis

The benefit-risk of rivaroxaban vs 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) (for details see Section 11.8).

TIME AND EVENTS SCHEDULE

Protocol Activity	Screen[a]	Randomize[b]	Treatment			30 Day F/U
	Screening	Day 1	Day 7	Day 21	Day 45 EOT[c]	Day 75 EOS
	Hospital/ Clinic/ Discharge Destination	Hospital/ Clinic/ Discharge Destination	Clinic/ Discharge Destination/ Telephone	Clinic/ Discharge Destination	Clinic/ Discharge Destination	Clinic/ Discharge Destination/ Telephone
Window			-2/+5d	-3/+7d	-0/+4d	-5/+5d
Informed Consent[d]	X					
Inclusion / Exclusion[e]	X	X				
VTE Risk[e]	X	X				
Physical Exam and Vitals[f]	X					
Demographics	X					
Medical History	X					
Hemoglobin/ Platelet count[g]	X					
Serum Creatinine[g]	X					
Serum/Urine Pregnancy[h]	X					
D-dimer (local)[i]	X					
Computed tomography/MRI of the head[j]	X					
IWRS Registration		X				
Dispense Study Drug		X		X[c]		
Index Hospitalization		X				
LMWH/UFH Use		X				
Clinical Assessment[f]		X		X	X	
Symptom Assessment			X	X	X	X
Subject Counseling[k]		X	X	X	X	
Study Drug Accountability				X	X	
Clinical Status/Suspected Outcomes			X	X	X	X
Adverse Events	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X
Medical Resource HECON			X	X	X	X
PK Sampling[l]			X	X		

Key: EOS=end of study; EOT=end of treatment; F/U=follow up; HECON= health economics; LMWH=low molecular weight heparin; MRI=magnetic resonance imaging; PK=pharmacokinetics; VTE=venous thromboembolism; IWRS= interactive web response system; UFH=unfractionated heparin.

a) Screening may begin any time, after the admission for the index hospitalization and once the informed consent is obtained. The index hospitalization must be at least 3 and no more than 10 consecutive days in duration.

b) Randomization should occur on the same day as or the day after the subject leaves the hospital.

c) The subject will be instructed to discontinue study drug after taking a dose on Day 45. ***Regardless of the day on which the Day 45 Visit occurs, no study drug may be taken after Day 45.***

d) A limited informed consent may be used for a screening local D-dimer or head computed tomography (CT) if permitted locally. Full informed consent must still be obtained before other study procedures are performed.

e) Screening inclusion / exclusion criteria and VTE risk score should be assessed and verified at randomization.

f) Vital signs include pulse and blood pressure. Physical exam will be performed at Screening or Randomization. Clinical Assessment is a focused evaluation of heart, lungs, lower extremities, and neurological status. If the physical examination is conducted at Day 1, then the Clinical assessment is not required on that day.

g) Hemoglobin, platelet count and serum creatinine must be obtained at least as recently as 2 days before the subject leaves the hospital or later, but before randomization.

h) Pregnancy test must be performed for women of child-bearing potential and may be repeated as indicated or required locally.

i) D-dimer may be obtained any time from the beginning of the index hospitalization up until randomization; the value obtained closest to the beginning of the index hospitalization should be used. A value >2xULN is required if the VTE risk score is 2 or 3.

j) Head CT/MRI performed only for subjects with ischemic stroke who received fibrinolytic agents; obtain at least 24 hours after fibrinolysis.

k) Includes training on the signs and symptoms associated with DVT, PE and bleeding and the appropriate response if symptoms develop.

l) Non-fasting PK samples will be obtained for subjects consented to participate at selected sites. For subjects participating in the PK assessment, the telephone visit option will not be applicable. For these subjects, visits at Day 7 and Day 21 must be conducted at the clinic.

At Day 7, 2 samples will be obtained: 1) pre-dose and 2) 1-4 hours post dose.

At Day 21, 2 samples at least 3 hours apart will be obtained: 1) 3-7 hours post-dose and 2) 7-12 hours post-dose.

ABBREVIATIONS

ACCP	American College of Chest Physicians
ACM	all-cause mortality
ACS	acute coronary syndrome
ASA	acetylsalicylic acid
AUC	area under the plasma concentration curve
AV	arteriovenous
BP	blood pressure
CCU	cardiac care unit
CEC	Clinical Event Committee
CHF	congestive heart failure
CI	confidence interval
CL/F	clearance
C_{max}	maximum serum concentration
C_{min}	minimum serum concentration
COPD	chronic obstructive pulmonary disease
CrCl	creatinine clearance
CT	computed tomography
CV	cardiovascular
CYP3A4	Cytochrome P450 3A4
DVT	deep vein thrombosis
eCRF	electronic case report form
eDC	electronic data capture
EC	Executive Committee
EF	ejection fraction
EOS	end of study
EOT	end of treatment
ER	emergency room
EU	European Union
FDA	Food and Drug Administration
FXa	factor Xa
GCP	Good Clinical Practice
HF	heart failure
HR	hazard ratio
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	intensive care unit
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMPROVE	International Medical Prevention Registry on Venous Thromboembolism (IMPROVE)
IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Haemostasis
ITT	intention-to-treat
IWRS	interactive web response system
Ka	first-order absorption rate constant
LC-MS/MS	liquid chromatography coupled to tandem mass spectrometry
LDUH	low-dose unfractionated heparin
LOS	length of stay
LMWH	low molecular weight heparin
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MRI	Magnetic resonance imaging
NT-proBNP	N-terminal pro-brain natriuretic peptide
P2Y12	G protein-coupled purinergic receptor P2Y
PE	pulmonary embolism
PK	pharmacokinetic

PP	per protocol
PPI	proton pump inhibitor
PQC	product quality complaint
RRR	relative risk reduction
SAP	statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
t_{max}	time to reach maximum concentration in plasma
TIA	transient ischemic attack
UFH	unfractionated heparin
ULN	upper limit of normal
US	United States
V/F	volume of distribution
VTE	venous thromboembolism

1. INTRODUCTION

Rivaroxaban is an oral, direct acting, Factor Xa (FXa) inhibitor anticoagulant that has been under development for the treatment of several thrombosis-mediated conditions. Rivaroxaban is marketed under the trade name XARELTO® and has been approved for multiple indications worldwide. The clinical development program for rivaroxaban is extensive. Over 70,000 subjects have been studied from Phase 1 through multiple large Phase 4 studies as of 15 March 2014, covering several indications and potential indications in the overall clinical development program. Over 40,000 of these subjects have been exposed to rivaroxaban in completed and ongoing company-sponsored interventional clinical trials and non-interventional studies, with the total daily doses of rivaroxaban ranging between 5 mg and 60 mg. In addition, rivaroxaban (10 mg daily) was evaluated for thromboprophylaxis in medically ill patients in the MAGELLaN trial[10].

For the most comprehensive nonclinical and clinical information regarding the efficacy and safety of rivaroxaban, refer to the latest version of the Investigator's Brochure[19].

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.

1.1. Background

Hemostasis is a normal physiological process following damage of the vascular system. In various diseases, however, the hemostatic mechanisms are inappropriately activated with pathological consequences known as thrombosis. Venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE) represents one of the most common health problems. More than 2 million Americans suffer from acute VTE each year. In the European Union (EU), incidence rates of DVT and PE are assumed to be slightly higher, but are generally consistent with those in the United States (US)[9,39]. Deep vein thrombosis and PE are a burden for healthcare systems as they are associated with high mortality and considerable morbidity in terms of recurrent events, the post-thrombotic syndrome, and chronic thromboembolic pulmonary hypertension [14,22,30,43]. Treatment of DVT and PE aims at prevention of worsening of the existing thrombus, as well as prevention of recurrent VTE[41].

Medically ill patients, ie, patients that are hospitalized for the treatment of acute medical illnesses, are at high risk for the development of VTE during their hospital stay and immediately after their hospital discharge. The American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines currently recommend anticoagulant thromboprophylaxis for acutely ill hospitalized medical patients with increased risk of thrombosis for 6 to 21 days, until full mobility is restored or until discharge from hospital, whichever comes first[20]. In the US and in many other countries including those in Europe, there is a growing trend for shorter hospital stays for patients hospitalized for medical conditions[1,29]. While continued thromboprophylaxis with parenteral agents post discharge could potentially reduce the overall risk of VTE, this approach has not yet been widely used, likely due to the challenges in administering a parenteral medication by the patient or caregivers and the lack of

compelling benefit-risk data with existing anticoagulants. The duration of thromboprophylaxis is largely determined by the duration of hospitalization and currently post-hospital thromboprophylaxis with parenteral agents is infrequently used, despite the fact that the risk of VTE persists after hospital discharge. Since the documented increase in risk of VTE persists well beyond hospital discharge, studies of extended thromboprophylaxis with oral anticoagulants in post-discharge patients hospitalized for medical conditions at risk for VTE are warranted[36].

Recently, 3 studies with extended treatment duration of enoxaparin (EXCLAIM), apixaban (ADOPT) and rivaroxaban (MAGELLaN) failed to demonstrate a positive benefit-risk profile for extended-duration thromboprophylaxis in patients hospitalized for medical conditions primarily due to increased bleeding with the anticoagulants[10,13,15,17].

The previous trial in medically ill patients (the MAGELLaN study) showed positive efficacy results of rivaroxaban but a bleeding risk that outweighed the benefit. Compared with this and the other trials, the MARINER trial was therefore modified to improve the overall safety of the subjects by addressing the bleeding risk observed in previous extended duration therapy studies while maintaining the efficacy that was observed. Several study design elements were modified to reduce the risk of major bleeding observed in the MAGELLaN study. Subjects with a baseline creatinine clearance (CrCl) of 30 to 49 mL/min have a higher risk for bleeding. Given that a relatively high number of medically ill patients with this lower CrCl will be enrolled, there will be a rivaroxaban dose adjustment for this subgroup. In addition, other high bleeding risk-subjects, eg, with active cancer or with clinically significant bleeding during index hospitalization, subjects who use 2 or more antiplatelet agents or acetylsalicylic acid (ASA) alone at a dose >162 mg/day or clopidogrel alone at a dose >75 mg/day will be excluded. None of the proposed measures, ie, dose alteration and exclusion of specific subgroups, is expected to reduce the efficacy of the overall study, but they are expected to reduce the risk of major bleeding in this population. Furthermore, in the present study, only hard efficacy outcomes (eg, symptomatic VTE [lower extremity DVT and non-fatal PE] events, VTE-related deaths [death due to PE or death in which PE cannot be ruled out as the cause]) will be assessed, compared with MAGELLaN, EXCLAIM, and ADOPT, where inclusion of asymptomatic proximal DVT as part of the primary efficacy outcome may have resulted in a less clinically meaningful evaluation (Section 3.2, Study Design Rationale). This Phase 3 clinical study with rivaroxaban is warranted to evaluate extended thromboprophylaxis up to 45 days after hospital discharge in medically ill subjects.

The proposed Phase 3 multicenter, prospective, randomized, double-blind, placebo-controlled, event-driven study is designed to evaluate rivaroxaban, compared with placebo, in the prevention of symptomatic VTE (lower extremity DVT and non-fatal PE) events and VTE-related deaths (death due to PE or death in which PE cannot be ruled out as the cause) for a period of 45 days post-hospital discharge in subjects ≥40 years of age who have been hospitalized for a specific acute medical illness and who have other risk factors for VTE. Prior to randomization, all subjects must have been prescribed thromboprophylaxis with low molecular weight heparin (LMWH) or unfractionated heparin (UFH) during the index hospitalization. If the treating physician believes that additional post-hospital discharge therapy with any anticoagulant is

clinically indicated, the patient will not be eligible for participation in the study. A dose adjustment to 7.5 mg daily will be implemented in high-risk medically ill subjects with CrCl ≥30 mL/min and <50 mL/min. The double-blind treatment duration will be 45 days followed by a 30-day follow-up period.

1.1.1. Compound Profile

As part of the prothrombinase complex, FXa directly converts prothrombin to thrombin. Thrombin converts fibrinogen to fibrin and activates platelets leading to clot formation. FXa occupies a critical place in the coagulation cascade since it is at the confluence of both the intrinsic and extrinsic clotting pathways, and is the key amplification point for the generation of thrombin. One molecule of FXa is able to generate more than 1,000 molecules of thrombin due to the amplification nature of the coagulation cascade. Selective inhibitors of FXa can terminate the amplified burst of thrombin generation and prevent clot formation.

Rivaroxaban is an oral, direct, FXa inhibitor anticoagulant. Rivaroxaban is rapidly absorbed after oral administration, with peak plasma concentrations occurring approximately 2 to 4 hours post dose. The elimination pathways of rivaroxaban include both hepatic and renal routes. The terminal elimination half-life of rivaroxaban is 5 to 9 hours in healthy young subjects and from 11 to 13 hours in healthy elderly subjects (aged 65 to 83 years). Due to the multiple elimination pathways of rivaroxaban, there are few clinically relevant drug-drug interactions.

Rivaroxaban has been under development and approved for the treatment of several thrombosis-mediated conditions. The clinical development program for rivaroxaban is extensive with over 70,000 subjects having been studied and includes data from clinical trials and post-marketing surveillance. Rivaroxaban is marketed under trade name XARELTO®.

1.1.2. Medically Ill Patients - Scope of the Problem

Medically ill patients, ie, patients that are hospitalized for the treatment of acute medical illnesses, are at high risk for the development of VTE during their hospital stay and immediately after their hospital stay. The rationale for the use of thromboprophylaxis is based on solid principles and scientific evidence [20]. Almost all hospitalized patients have at least one risk factor for VTE, and a high proportion have 3 or more risk factors. Without thromboprophylaxis, the incidence of objectively-confirmed, hospital-acquired DVT ranges from 10% to 40% among medical or general surgical patients and 40% to 60% following major orthopedic surgery. Thromboprophylaxis for the prevention of VTE in hospitalized medically ill patients is routinely prescribed and is recommended by internationally recognized guidelines[20]. Medically ill patients are generally defined as patients who are acutely hospitalized for 1 of the following diseases, including but not limited to, heart failure (HF) with reduced ejection fraction, respiratory conditions, acute infectious diseases, neurologic diseases, inflammatory and hematologic diseases, and cancer. Parenteral anticoagulation, including enoxaparin and UFH, are recommended for thromboprophylaxis in hospitalized medically ill patients, but thromboprophylaxis is not recommended after discharge [20].

1.1.3. Thromboprophylaxis in Patients with Acute Medical Conditions

Studies of short-term (10 to 12 days) thromboprophylaxis in medically ill patients showed a benefit for the LMWH enoxaparin administered during hospitalization (MEDENOX study), for the LMWH dalteparin administered for 14 days during and after hospital discharge (PREVENT study), and for the indirect Factor-Xa inhibitor fondaparinux administered during hospitalization (ARTEMIS study) over placebo[7,24,34].

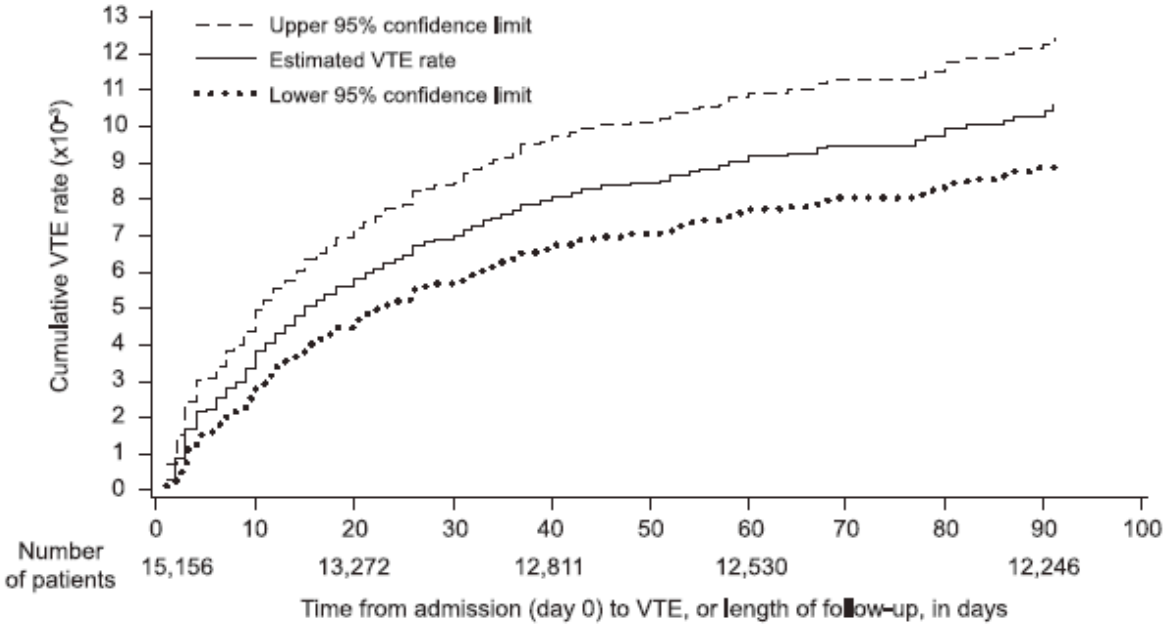
A meta-analysis of 4 studies of short-term enoxaparin treatment (treatment phase, 7 to 10 days) compared with UFH showed similarly a substantial reduction in VTE for enoxaparin compared with UFH in populations of hospitalized medically ill patients with acute respiratory disease, acute cardiovascular (CV) disease and acute ischemic stroke[23]. The combined incidence of VTE at Day 15 in this meta-analysis was 2.6% in the enoxaparin group and 5.2% in the UFH group; both rates are much lower than in untreated subjects. The combined major bleeding rate at Day 15 reported in the studies included in this meta-analysis was 0.65% for the enoxaparin-treated patients and 0.56% for the UFH-treated patients. Based on the clinical information available for acutely ill hospitalized medical patients at increased risk of thrombosis, the ACCP recommends anticoagulant thromboprophylaxis for 6-21 days, until full mobility is restored or until discharge from the hospital, whichever comes first[20]. Guidelines for post-hospital discharge specifically recommend against thromboprophylaxis.

1.1.4. VTE Risk Post Discharge in Patients Hospitalized for Medical Conditions

The risk of VTE persists after hospital discharge. More symptomatic VTEs have been diagnosed in the first 3 months following hospitalization than during the hospitalization phase[36]. It has been reported that in patients hospitalized for medical conditions, the cumulative symptomatic VTE incidence from admission to 3 months was 1% and stabilizes around 50 days (Figure 1)[37]. In this study, the median length of the hospitalization stay was 7 days.

Figure 1: Kaplan-Meier Curve Showing Cumulative Symptomatic VTE Incidence from Hospital Admission to 3 Months of Follow-up

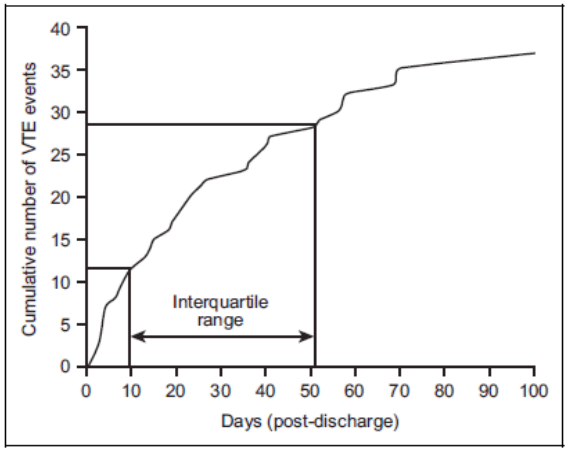
(n=15,156; n = 143 Patients with symptomatic VTE)



Source: From Spyropoulos et al., 2011[37]

Hull et al. (2013) demonstrated that in high risk patients 80% of the confirmed symptomatic VTE events (ie, DVT, PE) occurred within 57 days after hospital discharge and a VTE event rate of 2.7% was observed at 45 days post discharge[18]. Patients were classified as having VTE if the events were subsequently confirmed by diagnostic testing. High risk patients were defined as >60 years of age and having at least 1 of the following risk factors: history of malignancy, respiratory illness, neurological illness, inflammatory bowel disease, previous VTE, acute infection, or heart failure. Over the 100 day follow-up, 3.8% of the 989 patients had a confirmed VTE event (Figure 2) [18].

Figure 2: Cumulative Number of Events Over Time: High-risk Elderly Medical Patients.



Source: Hull et al., 2013[18]

1.1.5. Studies Examining Extended Thromboprophylaxis in Patients Hospitalized for Acute Medical Conditions and MARINER Approach

While extended-duration (4-week) thromboprophylaxis has been shown to significantly reduce the incidence of VTE compared with a standard (1-week) regimen in high-risk surgical patients, extended duration thromboprophylaxis has not been shown to be of value in patients hospitalized for medical conditions. Medical patients represent most hospitalized patients and at least 75% of fatal pulmonary emboli occur in this group[5,8,12,16,31].

In the MAGELLaN study, the primary efficacy endpoint was a composite of events of: 1) asymptomatic proximal DVT in a lower extremity detected by mandatory bilateral lower extremity venous ultrasonography, 2) symptomatic DVT in a lower extremity, proximal or distal, 3) symptomatic, non-fatal PE, and 4) VTE-related death. VTE-related death was defined as either a well-documented fatal PE, or sudden death with no other plausible explanation. The study compared VTE prophylaxis with oral rivaroxaban 10 mg once daily for 35 days with enoxaparin 40 mg daily for 10 days in subjects who were hospitalized for a medical illness. The MAGELLaN study met both of its protocol-specified primary efficacy outcomes for rivaroxaban versus enoxaparin/placebo at both Day 10 (non-inferiority) and Day 35 (superiority). At Day 35, at the end of the rivaroxaban-enoxaparin/placebo phase (treatment phase), rivaroxaban was statistically significantly superior to enoxaparin in the mITT Day 35 population (two-sided p=0.0211). The RR was 0.77 with the 95% confidence interval (CI) ranging from 0.62 to 0.96. The incidence rate of the primary efficacy composite outcome events at Day 35 was higher in the enoxaparin group (5.7% [175/3057]) than in the rivaroxaban group (4.4% [131/2967]) (mITT Day 35 population). At Day 10, at the end of the rivaroxaban-enoxaparin phase (active control treatment phase), rivaroxaban was demonstrated to be non-inferior to enoxaparin in the per protocol (PP) population (statistically significant with a one-sided p=0.0025). The RR was 0.97 with a 95% CI ranging from 0.71 to 1.31. The incidence rate of the primary efficacy composite outcome events at Day 10 was identical in both treatment groups in the PP Day 10 population (rivaroxaban, 2.7% [78/2938]); enoxaparin, 2.7% [82/2993]). However, rivaroxaban also increased major bleeding events.

The CIs and p-values for the weighted relative risks of bleeding events in the 3 treatment phases were statistically significant in favor of enoxaparin. By phase, the major bleeding events in the rivaroxaban-enoxaparin/placebo phase (Day 1 to Day 35) were reported in 43 (1.1%) vs 15 (0.4%) subjects, in the rivaroxaban-enoxaparin phase (Day 1 to Day 10) in 24 (0.6%) vs 11 (0.3%) subjects, in the rivaroxaban-placebo phase (Day 10 to 35) in 19 (0.5%) and 4 (< 0.1%) subjects in the rivaroxaban and enoxaparin groups, respectively.

The EXCLAIM study (Extended prophylaxis for VTE in acutely ill medical patients with prolonged immobilization), compared an extended duration (28 days) enoxaparin with placebo in patients recently hospitalized for acute medical illnesses who received enoxaparin during their initial hospital stay[17]. The extended-duration enoxaparin treatment was found to reduce the incidence of VTE compared with placebo (2.5% vs. 4%; absolute risk difference favoring enoxaparin, -1.53% [95.8% CI, -2.54% to -0.52%]). However, enoxaparin also increased major bleeding events (0.8% vs. 0.3%; absolute risk difference favoring placebo, 0.51% [95% CI,

0.12% to 0.89%]). As such, the benefit-risk balance of VTE thromboprophylaxis was not positive for the patients studied and enoxaparin is not approved for extended use in this population.

The ADOPT study (Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients) compared an extended duration (30 days) of 2.5 mg twice daily oral apixaban with enoxaparin, administered subcutaneously at a dose of 40 mg daily for 6 to 14 days [15]. Based on the results of the primary efficacy endpoint (the composite of death related to VTE, PE, symptomatic DVT or asymptomatic proximal-leg DVT at Day 30) extended duration thromboprophylaxis with apixaban was not superior to a shorter duration of thromboprophylaxis with enoxaparin (2.71% vs. 3.06%; relative risk [RR] 0.87; 95% CI, 0.62 to 1.23). Major bleeding events during the 30 day treatment period occurred in 0.47% of the patients in the apixaban group and in 0.19% of the patients in the enoxaparin group (RR 2.58; 95% CI, 1.02 to 7.24). The primary efficacy endpoint was not positive in this study and apixaban is not approved for this indication.

The increased bleeding associated with extended duration of therapy was seen in all 3 studies, MAGELLaN, EXCLAIM and ADOPT. Any new clinical study purporting to evaluate extended duration of antithrombotic therapy must address this observed hazard. One potential means to diminish the excess bleeding rates would be to identify those patients with a more positive benefit/risk profile. Post-hoc analysis of the MAGELLaN study indicated that those who experienced a bleeding event while hospitalized or patients with active cancer were at higher risk of bleeding and are therefore excluded from MARINER.

The selection of a high VTE-risk population is also important for the demonstration of a positive benefit/risk with anticoagulant therapy. Since the completion of the pivotal Phase 3 studies of extended thromboprophylaxis in hospitalized medical patients, there has been extensive research in the use of clinical VTE-risk assessment models as well as biomarkers in helping to define a high VTE-risk group in this patient population.[3,10,26,33] In this regard, the MARINER study is relying on an evidence-derived, weighted, and scored clinical VTE-risk score, the IMPROVE VTE-risk score, alone or in combination with an elevated D-dimer to enroll a sufficiently high VTE-risk cohort when compared to previous studies that would benefit from extended thromboprophylaxis. The IMPROVE VTE-risk score has been extensively validated in 2 large external validation studies and a D-dimer >2X the upper limit of normal (ULN) was shown to be a powerful predictor of VTE in the general patient population of the MAGELLaN study as well as the subgroup with CHF.[11, 31, 25,26]

As MARINER will be assessing only symptomatic events it will be critical to study conduct to ensure all efficacy events are appropriately captured. Pulmonary embolism (PE) has been reported as the most common missed or delayed diagnosis by physicians.[35,41] Misdiagnosis of PE has been shown in the literature to occur in up to 50% of patients with PE.[2] Reports show that PE can be misdiagnosed as pneumonia, bronchitis, heart failure, cardiorespiratory failure, exacerbation of chronic obstructive pulmonary disease (COPD) and other diagnoses.[2,32,12] A meta-analysis of the prevalence of PE in acute exacerbations of COPD concluded that 25% of COPD patients who require hospitalization for acute exacerbation and 9% of patients

hospitalized with severely decompensated heart failure may have a PE.[32, 12] Both study staff and subjects will be educated on signs and symptoms associated with PE.

1.2. Overall Rationale for the Study

The primary objective is to assess the efficacy and safety of rivaroxaban, compared with placebo in the prevention of symptomatic VTE (lower extremity DVT and non-fatal PE) and VTE-related death (death due to PE or death in which PE cannot be ruled out as the cause) post-hospital discharge in high-risk medically ill subjects.

Three extended duration studies with enoxaparin (EXCLAIM), apixaban (ADOPT) and rivaroxaban (MAGELLaN) failed to demonstrate a positive benefit/risk profile for extended-duration thromboprophylaxis in patients hospitalized for medical conditions primarily due to excessive bleeding with the anticoagulants[10,15,17].

Therefore, the proposed MARINER study was designed to improve the overall safety of medically ill patients with rivaroxaban (10 mg daily in subjects with CrCl ≥50 mL/min or 7.5 mg daily in subjects with CrCl of ≥30 to <50 mL/min) treatment for 45 days post-hospital discharge by addressing the bleeding risk observed in the MAGELLaN study while also enrolling a higher VTE-risk population to enhance the overall expected benefit/risk assessment. The proposed study is a multicenter, prospective, randomized, double-blind, event-driven, placebo-controlled study in subjects who are hospitalized for a specific acute medical illness and have other risk factors for VTE. In the proposed study, a specific population of medically ill patients at high risk who could benefit most from extended thromboprophylaxis has been identified.

The MARINER study is designed as a pivotal Phase 3 study, to determine if the use of the FXa inhibitor rivaroxaban can prevent symptomatic VTE (lower extremity DVT and non-fatal PE) and VTE-related death post-hospital discharge in high-risk, medically ill patients.

2. OBJECTIVES AND HYPOTHESES

2.1. Objectives

Primary Objective

- The primary objective is to assess the efficacy and safety of rivaroxaban, compared with placebo in the prevention of symptomatic VTE (lower extremity DVT and non-fatal PE) and VTE-related death (death due to PE or death in which PE cannot be ruled out as the cause) post-hospital discharge in high-risk, medically ill patients.

Secondary Objectives

The secondary objectives are to compare rivaroxaban with placebo in the following post-hospital discharge outcomes in high-risk, medically ill patients:

- VTE-related death (death due to PE or death in which PE cannot be ruled out as the cause)
- Symptomatic VTE (lower extremity DVT and non-fatal PE)
- The composite of symptomatic VTE (lower extremity DVT and non-fatal PE) and all-cause mortality (ACM)
- The composite of symptomatic VTE (lower extremity DVT and non-fatal PE), MI, non-hemorrhagic stroke and CV death (death due to a known CV cause and death in which a CV cause cannot be ruled out; by this definition, a VTE-related death is considered a CV death)
- ACM

Exploratory Objectives

The exploratory objectives are to compare rivaroxaban with placebo, in the following post-hospital discharge outcomes in high-risk, medically ill patients:

- Symptomatic lower extremity DVT
- Symptomatic non-fatal PE
- Symptomatic upper extremity DVT
- MI
- Non-hemorrhagic stroke
- Re-hospitalization for symptomatic VTE (lower extremity DVT and non-fatal PE) within 30 days after randomization

Pharmacokinetic Objective

The pharmacokinetic objective (PK) is to assess the kinetics of rivaroxaban in high-risk, medically ill patients, and to describe drug exposure based on CrCl.

Medical Resource Utilization and Health Economics Objective

The medical resource utilization and health economics objective is to assess the following cost drivers, ie, re-hospitalization (including ER visits, intensive care unit and cardiac care unit stays), length of stay and subject discharge destination (after re-hospitalization).

Safety Objectives

The safety objectives are to compare rivaroxaban with placebo in the following bleeding outcomes in high-risk, medically ill patients:

- Major bleeding using validated International Society on Thrombosis and Haemostasis (ISTH) bleeding criteria.
- Non-major clinically relevant bleeding
- Other bleeding

Overall safety will also be assessed.

2.2. Hypotheses

The primary hypothesis is that rivaroxaban is superior to placebo in the prevention of the composite of symptomatic VTE (lower extremity DVT and non-fatal PE) and VTE-related death (death due to PE or death in which PE cannot be ruled out as the cause). The secondary hypotheses are that rivaroxaban is superior to placebo in the prevention of 1) VTE-related death (death due to PE or death in which PE cannot be ruled out as the cause), 2) symptomatic VTE (lower extremity DVT and non-fatal PE), 3) the composite of symptomatic VTE (lower extremity DVT and non-fatal PE) and ACM, 4) the composite of symptomatic VTE (lower extremity DVT and non-fatal PE), MI, non-hemorrhagic stroke and CV death (death due to a known CV cause and death in which a CV cause cannot be ruled out; by this definition, a VTE-related death is considered a CV death) and 5) ACM alone.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a multicenter, prospective, randomized, double-blind, placebo-controlled, event-driven study designed to evaluate rivaroxaban, compared with placebo, in the prevention of symptomatic VTE (lower extremity DVT and non-fatal PE) events and VTE-related deaths (death due to PE or death in which PE cannot be ruled out as the cause) for a period of 45 days post-hospital discharge. The study consists of a screening phase, a 45-day double-blind treatment phase, and a 30-day safety follow-up period.

The subject population comprises men and women age 40 years and older who have completed screening no later than 1 day after leaving the hospital and who have been hospitalized for the new onset or exacerbation of 1 of the following medical conditions:

- Heart Failure (HF) with a reduced left ventricular ejection fraction (LVEF ≤45%)
- Acute respiratory insufficiency or acute exacerbation of COPD
- Acute ischemic stroke (including spinal cord infarction if no evidence of intramedullary, subdural or epidural hemorrhage)
- Acute infectious disease
- Inflammatory disease, including rheumatic disease

The index hospitalization must be at least 3 and no more than 10 consecutive days in duration. In order to be eligible, subjects must have an increased VTE risk, as demonstrated by a total modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) VTE Risk Score of:

- ≥ 4, or
- 3 with D-dimer > 2XULN, or
- 2 with D-dimer > 2XULN

In addition, subjects must have received treatment during the index hospitalization with LMWH or UFH.

Any patient with a medical condition that will require use of any parenteral or oral anticoagulation (eg, atrial fibrillation) during the study is not eligible for participation. In addition, patients at particularly increased risk of bleeding and those using medications that might interact with the study drug will be excluded.

Subjects who meet all of the inclusion and none of the exclusion criteria will be randomly assigned to receive rivaroxaban or placebo. Randomization should occur on the same day as or the day after the subject leaves the hospital, and may occur at the hospital, clinic or other discharge destination. Subjects will be randomized by strata including creatinine clearance and country.

After randomization, subjects will receive double-blind treatment with rivaroxaban 10 mg (7.5 mg for subjects with a CrCl ≥30 mL/min and <50 mL/min) daily or matching placebo daily. Placebo has been chosen as the comparator because of current guidelines which recommend against thromboprophylaxis in medically ill patients after hospital discharge. The first dose of study drug should be administered no later than the day after the subject leaves the hospital and as soon after randomization as possible. Subjects will be instructed to discontinue study drug after they take a dose on Day 45, and complete an end of treatment visit within the next 4 days. ***Regardless of the day on which the Day 45 Visit occurs, no study drug may be taken after Day 45.*** The subject must be assessed 30 days later for safety follow-up. This will be the last contact with the subject unless extended follow up for safety is required.

If a subject has a suspected efficacy or bleeding outcome event during the study, the treating physician should exercise clinical judgment and follow established guidelines to apply the standard of care. Unblinding of study drug should not be necessary. Anticoagulation regimens do not require adjustment regardless of treatment group assigned when study drug is placebo vs rivaroxaban when administered in the doses used in this study. There is no specific reversal agent for rivaroxaban; management of the subject with a bleeding event should not be impacted by knowledge of study drug treatment.

Rivaroxaban will not be provided to subjects after they complete study treatment unless required by local regulations. Randomization in this study is preceded by a hospitalization for an acute illness and the study drug treatment phase extends for 45 days after randomization to correspond to the period of greatest risk for VTE. Chronic therapy with the study drug is not being tested. It will only be after data from the entire study is analyzed that it will be determined if the population at risk will benefit from treatment.

The primary efficacy outcome is the composite of all symptomatic VTE events (lower extremity DVT and non-fatal PE) and VTE-related death (death due to PE or death in which PE cannot be ruled out as the cause), from randomization up to Day 45. The targeted total number of primary efficacy outcomes in this event-driven study is 161. It is estimated that a total of approximately 8,000 subjects will need to be randomized to either rivaroxaban or placebo in a 1:1 ratio. In the event that the actual observed blinded pooled event rate is lower than the assumed rate, more subjects may be enrolled to accumulate additional outcome events. Randomization in this study may be stopped at approximately 12,000 subjects for administrative considerations even if the targeted 161 events have not been observed by then. An interim analysis for futility will be conducted when approximately 50% of subjects with adjudicated primary efficacy outcome events have been observed (about 50% of the expected total number of events based on the actual observed blinded pooled event rate even if this event rate is lower than the assumed rate).

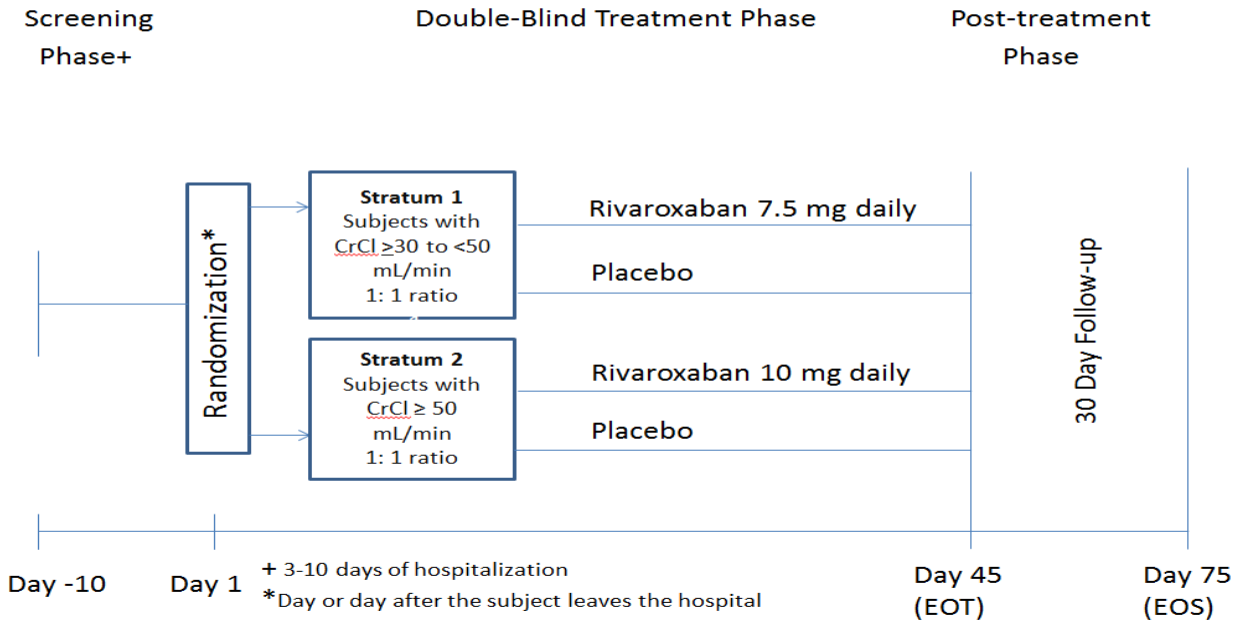
The principal safety outcome for this study is ISTH major bleeding.

For population PK analyses, based on the model performance and the high variability of the PK parameters observed in the MAGELLaN study, 2 blood samples (at pre-dose and 1-4 hours after study drug administration) will be collected at the Day 7 visit and 2 blood samples (at 3 to 7 and 7 to 12 hours after study drug administration) will be collected at the Day 21 visit for each subject for up to 600 subjects (300 rivaroxaban subjects [200 subjects in the 10 mg daily group and 100 subjects in the 7.5 mg daily group] and 300 in the placebo group). The sparse blood samples for PK analyses will be collected in selected sites only.

An Executive Committee (EC), an Independent Data Monitoring Committee (IDMC) and a Clinical Event Committee (CEC) will be commissioned for this study. All committees will be governed by separate charters, see Section 3.3.

A diagram of the study design is provided below in Figure 3:

Figure 3: Schematic Overview of the Study (RIVAROXDVT3002)



Note: Subjects will be randomized by strata including creatinine clearance and country.

3.2. Study Design Rationale

Study Population

Medically ill patients, ie, patients who have been hospitalized for the treatment of acute medical illnesses, are at high risk for the development of VTE during their hospital stay and immediately after hospital discharge. These are important clinical events that profoundly impact medically ill patients, and constitute a large burden in terms of health care provision. High-risk medically ill subjects have been chosen for this study because post-hospital discharge thromboprophylaxis is a useful therapeutic approach to reduce the risk of increased VTE events, morbidity and mortality in these patients and would meet an unmet medical need. The pharmacology, mechanism of action, and previous clinical studies of rivaroxaban suggest that rivaroxaban will reduce the risk of VTE events and VTE-related death (death due to PE or death in which PE cannot be ruled out as the cause). The timing of enrollment, randomization and treatment phase for these subjects has been chosen because there is a high rate of VTEs and VTE-related mortality during this post-hospitalization phase, particularly during the first 2 months after discharge[18,37]. Compared with previous studies, there are several differences in the choice of study populations to reduce the bleeding risk (Section 1.1).

Blinding Control Study Phase/Periods Treatment Groups

This randomized, double-blind, placebo-controlled, parallel-group, multicenter, event-driven design, is a scientifically rigorous approach for evaluating the efficacy and safety of rivaroxaban in high-risk, medically ill patients and meets the registration requirements for a superiority study.

Randomization and stratification will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes

(eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Subjects will be randomized by strata (by subjects with CrCl ≥30 mL/min and <50 mL/min versus subjects with CrCl ≥50 mL/min, and by country). Double-blinded treatment will be implemented to reduce potential bias during data collection and evaluation of clinical outcomes.

There has been no well-controlled study to date that demonstrates any anticoagulant with a favorable benefit/risk profile (reduction of symptomatic VTE events and VTE-related mortality vs increase in major bleeding) in post-discharge high-risk medically ill patients.

Comparator Selection

The control group in the MARINER study will receive placebo, a decision that was made based on careful consideration of the literature and existing guidelines for the standard of care practice.

Medically ill patients are at risk for the development of VTE both when hospitalized and immediately after their hospital discharge. These 2 periods of risk have been studied, are reported in the literature, and the ACCP has published thromboprophylaxis guidelines. Guidelines have been published for the inpatient period, and also for the post-hospital discharge period.

For inpatients, the ACCP recommends:

> "For acutely ill hospitalized medical patients at increased risk of thrombosis, we recommend anticoagulant thromboprophylaxis with LMWH, low-dose unfractionated heparin (LDUH) bid, LDUH tid, or fondaparinux (Grade 1B)."

For post-hospital discharge, the ACCP recommends (emphasis added):

> "In acutely ill hospitalized medical patients who receive an initial course of thromboprophylaxis, we suggest ***against extending the duration of thromboprophylaxis*** beyond the period of patient immobilization or acute hospital stay."

The ACCP Evidence-Based Clinical Practice Guidelines further recommend that during hospitalization, anticoagulant thromboprophylaxis for acutely ill hospitalized medical patients with increased risk of thrombosis should be administered for 6 to 21 days (an evidence-based duration derived from the range of the durations of therapies studied and reported in the literature). However, if full mobility is restored while hospitalized or the patient is discharged from the hospital, the recommendation is that thromboprophylaxis be discontinued. As such, the guidelines recommend that patients not receive thromboprophylaxis after discharge.

As described in Section 1.1.5, 3 studies have been conducted testing an extended period of thromboprophylaxis. For each of these studies, a post-hospital discharge placebo comparator was used, and none provided evidence of a benefit/risk balance better than placebo. The MARINER study will enroll a population at greater risk of VTE and lower risk of bleeding than previously studied, and will use the placebo comparator as the standard of care, as recommended by the

ACCP. Given the ACCP guidelines, the duration of thromboprophylaxis in these patients is usually determined by the duration of hospitalization, as it is unusual for patients to receive thromboprophylaxis after discharge. In fact, in the MARINER study, patients for whom thromboprophylaxis is prescribed after discharge are specifically excluded.

Based on the above, placebo has been chosen as the appropriate comparator to allow for the evaluation of benefit/risk of rivaroxaban as thromboprophylactic agent in post-hospital discharge high-risk, medically ill patients.

Any patient with a medical condition that will require chronic use of any parenteral or oral anticoagulation (eg, atrial fibrillation) during the study is not eligible for participation. During the study, should the subject develop any condition, which in the investigator's judgment requires long-term anticoagulation, thromboprophylaxis, or fibrinolysis, the subject will have study treatment either temporarily interrupted or permanently discontinued and will be managed as deemed appropriate by the treating physician. The subject will be asked to continue in the study to be followed for efficacy and safety outcomes.

Dose Selection

The selection of a dose of 10 mg daily of rivaroxaban is based primarily on the results of the studies conducted for prophylaxis of VTEs in patients undergoing knee or hip replacement surgery, where 10 mg daily of rivaroxaban resulted in benefit with an acceptable risk profile.

Subjects with CrCl ≥50 mL/min will be randomly assigned to receive rivaroxaban 10 mg daily or placebo. In order to reduce the risk of bleeding in subjects with a baseline CrCl ≥30 mL/min and <50 mL/min (estimated to be approximately 20% of study population), a dose adjustment of rivaroxaban from 10 mg daily to 7.5 mg daily will be implemented (Section 3.1)

In the ROCKET AF study, a 25% dose reduction of rivaroxaban (15 mg daily) was implemented in subjects with CrCl 30 to 49 mL/min (approximately 20% of the study population), which provided comparable exposure, efficacy and safety to that of rivaroxaban 20 mg daily administered to subjects with CrCl ≥50 mL/min[29]. Since the age and comorbidities of the subjects in the proposed MARINER study are similar to the population studied in the ROCKET AF study and based on the population PK simulations of a virtual medically ill population, a similar 25% dose reduction of rivaroxaban (from 10 mg to 7.5 mg daily) in the subjects with CrCl ≥30 mL/min and <50 mL/min is a reasonable strategy. This rivaroxaban dose reduction in medically ill subjects with CrCl ≥30 mL/min and <50 mL/min is predicted to yield similar rivaroxaban plasma exposures to those in subjects with CrCl ≥50 mL/min at a 10 mg dose. Based on the achievement of similar plasma exposures, comparable efficacy and safety would be expected in these 2 population subgroups.

Choice of Efficacy Measure

The choice of the primary efficacy outcome is based on prior rivaroxaban trials for primary and secondary prevention of VTE events (such as DVT, PE) and VTE-related deaths. In addition, these outcomes are considered acceptable and verifiable for the evaluation of prevention of VTE events in medically ill patients[10,15,18].

Asymptomatic proximal DVT, as detected on compression ultrasonography, was included as part of the primary efficacy outcome in the 3 extended-duration studies (EXCLAIM, ADOPT and MAGELLaN). Compression ultrasonography is not performed routinely in medical patients and the use of this test might influence the symptomatic VTE component of the primary efficacy composite outcomes[15]. Specifically, the performance of compression ultrasound during double-blind treatment likely influences the subsequent natural history of the disease by prompting investigators to treat asymptomatic clots. Therefore, without asymptomatic clot detection there will be a higher symptomatic event rate and assessment of only symptomatic events may provide a more clinically meaningful evaluation of a therapeutic intervention. Thus, in the present study only hard efficacy outcomes (symptomatic VTE events, VTE-related deaths, etc.) will be measured.

Choice of Safety Measures

The principal safety outcome is major bleeding using validated ISTH bleeding criteria.

In addition, data will be collected to ascertain non-major clinically relevant bleeding, 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 treatment, or associated with discomfort for the subject such as pain or impairment of activities of daily life, and other bleeding, defined as any other overt bleeding that does not meet the ISTH criteria for major or non-major clinically relevant bleeding (Section 9.5).

All serious adverse events except the study outcomes (VTE-related death, MI, acute coronary syndrome [ACS], stroke, transient ischemic attack [TIA], symptomatic VTE [lower or upper extremity DVT and PE], bleeding events) will be collected. Refer to Section 12.3.1, All Adverse Events for more details.

Interim Analysis

The primary reason for the prespecified interim analysis is to assess for futility.

Pharmacokinetics Analysis

The PK analysis will be done:

- To predict the overall exposure of rivaroxaban and estimate the PK model parameters for medically ill patients.
- To describe the effect of dosing modification on exposure for subjects with CrCl ≥30 mL/min and <50 mL/min.

Medical Resource Utilization and Health Economics

The medical resource utilization and health economics will assess cost drivers and details on medical resource utilization and health economics can be found in Section 9.4.

3.3. Committees

3.3.1. Executive Committee

The EC consists of members of the academic leadership of the study and 1 member 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.

3.3.2. Independent Data Monitoring Committee

An IDMC will be established to monitor the progress of the study and ensure that the safety of subjects enrolled in the study is not compromised. The IDMC will include, but is not limited to, a clinical chairman, physician(s) experienced in clinical trials, 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 interim analysis and make a recommendation whether the study should be continued as planned, modified, or terminated prematurely due to futility or safety (Section 11.7).

3.3.3. Clinical Events Committee

The Clinical Events Committee (CEC) is comprised of board-eligible or board-certified specialist physicians as appropriate and necessary. Committee members do not directly enroll subjects in the study, are not involved in the MARINER study monitoring, and do not have direct operational responsibilities for the conduct of the study. Members will review all suspected outcome events as described below that occurred post-randomization as they become available and adjudicate and classify in a consistent and unbiased manner according to definitions in the CEC charter while blinded to treatment assignment:

- Death
- Symptomatic DVT
- Symptomatic non-fatal PE

- Non-fatal MI
- Non-fatal stroke
- Bleeding

4. SUBJECT POPULATION

Screening may begin any time after the admission for the index hospitalization, and once the informed consent is obtained. If a subject's status changes (including laboratory results or receipt of additional medical records) after screening but before randomization such that he or she no longer meets all eligibility criteria, then the subject should not be randomized.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate sponsor representative before enrolling a subject in the study. Waivers for study participation will not be granted.

For Sections 4.1, Inclusion Criteria, 4.2, Exclusion Criteria, and 4.3, Prohibitions and Restrictions, numbered criteria in brackets are for data collection purposes and are intentionally non-sequential (for complete amendment history, see Attachment 6).

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study.

- **[1.2]**

  a. Subject must be a man or woman, ≥40 years of age.

  b. The duration of the index hospitalization must have been at least 3 and no more than 10 consecutive days.

  The index hospitalization is defined as a hospitalization that ended on the day of or the day before randomization and is a continuous period of time at an acute care facility (including hospital, observation unit, ER and/or transferring facility; collectively referred to as "hospital"). The first day that the subject spends any part of the day in the hospital will be counted when determining the duration of the index hospitalization, but the day the patient leaves the hospital will not be counted.

  c. The reason for the index hospitalization must have been a new diagnosis or exacerbation of 1 of the following medical conditions:

  - Heart Failure (HF)

    Subject must have a documented LVEF ≤45% within 1 year before randomization or during the index hospitalization. The ejection fraction may be determined by one of the following methods: echocardiogram, nuclear multi-gated acquisition (MUGA) scan, cardiac magnetic resonance imaging (MRI), cardiac computed tomography (CT) scan, or left ventriculography). If more than 1 value for LVEF is available, the most recent one should be used.

  - Acute respiratory insufficiency or acute exacerbation of COPD

- Acute ischemic stroke (including spinal cord infarction if no evidence of intramedullary, subdural or epidural hemorrhage)

  If the subject received fibrinolysis as part of the initial treatment for stroke, fibrinolysis must have been administered at least 3 full days before the subject is randomized. These subjects must have had a CT/MRI scan at presentation and a repeat scan performed at least 24 hours after administration of fibrinolysis that documents the absence of hemorrhage. Subjects with hemorrhagic transformation of an ischemic infarct prior to randomization are not excluded unless there is evidence of parenchymal hemorrhage (types PH-1 and PH-2). All planned diagnostic tests for stroke evaluation must be completed before randomization. Brain imaging and 24-hour cardiac monitoring must have been repeated if new symptoms of stroke/TIA occurred after the initial stroke evaluation, as does 24-hour cardiac monitoring if symptoms suggestive of AF occur.

- Acute infectious disease
- Inflammatory disease, including rheumatic disease

➢ **[2.2]** The subject must be at increased risk for VTE by the total modified IMPROVE VTE Risk Score (Table 1; modified from Spyropoulos[37]) assessed at screening and verified at randomization.

a. If the total modified IMPROVE VTE Risk Score is ≥4, the subject meets this inclusion criterion.

b. If the total modified IMPROVE VTE Risk Score is 2 or 3, a D-dimer >2X ULN must have been obtained after the beginning of the index hospitalization and before randomization

Table 1: Modified IMPROVE VTE Risk Score

VTE Risk Factor	VTE Risk Score
Previous VTE	3
Known thrombophilia[a]	2
Current lower limb paralysis or paresis[b]	2
History of cancer[c]	2
ICU/CCU stay	1
Complete immobilization[d] ≥1 day	1
Age ≥60 years	1

CCU= cardiac care unit; ICU= intensive care unit; VTE= venous thromboembolism.
a: A congenital or acquired condition leading to excess risk of thrombosis (eg, factor V Leiden, lupus anticoagulant, factor C or factor S deficiency).
b: Leg falls to bed by 5 seconds, but has some effort against gravity (taken from NIH stroke scale[28]).
c: Cancer (excluding non-melanoma skin cancer) present at any time in the last 5 years (cancer must be in remission to meet eligibility criteria)
d: Immobilization is being confined to bed or chair with or without bath-room privileges.

➢ **[3.1]** Life expectancy of at least 3 months.

- **[4.3]** Prescribed thromboprophylaxis (according to ACCP guidelines)[20] with UFH or LMWH (eg, dalteparin and enoxaparin) not exceeding 15,000 U on any given day for UFH and not exceeding 5,000 U on any given day for LMWH.

Table 2 below provides the minimum number of doses of thromboprophylaxis required by index hospitalization duration. For ischemic stroke with thrombolysis, do not use the index hospital duration to determine the number of doses required. Instead, use the number of days the patient was in the hospital after the first day the patient was prescribed thromboprophylaxis.

Table 2: Minimum Number of Heparin Doses Required for Study Eligibility by Duration of Index Hospitalization

Index Hospitalization Duration (days)	LMWH doses required	UFH doses required
3	2	3
4	2	4
5	3	6
6	4	7
7	4	8
8	5	10
9	6	11
10	6	12

LMWH= low molecular weight heparin, UFH= unfractionated heparin.

Note: In the event that both LMWH and UFH are used during the index hospitalization, the number of doses of LMWH received should be doubled and added to the number of UFH doses received, and the UFH doses required column should be used to determine whether the requirement was met.

- **[6.1]** Each subject must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study.

Note: Numbered criteria in brackets are for data collection purposes and are intentionally non-sequential.

4.2. Exclusion Criteria

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

Bleeding Risk-Related Criteria

- **[1.1]** Any bleeding (defined as bleeding requiring hospitalization, transfusion, surgical intervention, invasive procedures, occurring in a critical anatomical site, or causing disability) within 3 months prior to randomization or occurring during index hospitalization.

- **[2.3]** Major surgery, biopsy of a parenchymal organ, ophthalmic surgery (excluding cataract surgery), or serious trauma (including head trauma) within 4 weeks before randomization.

  Investigator discretion should be applied, but the following guidance may be considered for the purpose of this study.

  ***Major surgery** often involves opening 1 of the major body cavities the abdomen, the chest, or the skull and can stress vital organs. Major surgery usually is done using general anesthesia in a hospital operating room by a surgeon(s) and usually requires a stay of at least 1 night in the hospital after surgery.*

  *In contrast, with **minor surgery**, major body cavities are not opened. Minor surgery can involve the use of local, regional, or general anesthesia and may be done in an emergency department, an ambulatory surgical center, or a doctor's office. Vital organs usually are not stressed, and surgery can be done by a single doctor, who may or may not be a surgeon. Usually, the person can return home on the same day that minor surgery is done.*

  *Investigator discretion should be applied, but fracture or concussion would be considered **serious head trauma**, while external trauma without fracture or concussion could be considered for inclusion.*

- **[3.3]** Any planned major surgery (see exclusion criterion #2.3) or major invasive diagnostic procedure intended during the duration of the trial.

- **[4.1]** Subjects with any known coagulopathy or bleeding diathesis, or an INR >1.5 during the index hospitalization without a subsequent value (the last value before randomization) that is ≤ 1.5.

- **[5.2]** A history of hemorrhagic stroke or any intracranial bleeding at any time in the past, evidence of primary intracranial hemorrhage on CT or magnetic resonance imaging scan of the brain, or clinical presentation consistent with intracranial hemorrhage. This applies as well to subjects hospitalized for ischemic stroke upon randomization.

  Subjects with hemorrhagic transformation of an ischemic infarct prior to randomization are not excluded unless there is evidence of parenchymal hemorrhage (types PH-1 and PH-2):

  Hemorrhagic infarction type 1 (HI-1) is defined as small petechiae along the margins of the infarct, and HI type 2 (HI-2) is defined as more confluent petechiae within the infarcted area but without space-occupying effect. PH type 1 (PH-1) is defined as hematoma in ≤30% of the infarcted area with some slight space-occupying effect; PH type 2 (PH-2) is defined as dense hematoma >30% of the infarcted area with substantial space-occupying effect or as any hemorrhagic lesion outside the infarcted area (Berger, 2001[2]).

  Hemorrhagic infarction type 1 and HI-2 subjects are NOT excluded from this study, but PH-1 and PH-2 subjects ARE excluded from this study.

- **[7.1]** Subject has a history of or current intracranial neoplasm (benign or malignant), cerebral metastases, arteriovenous (AV) malformation, or aneurysm.

- **[8]** Active gastroduodenal ulcer, defined as diagnosed within 3 months or currently symptomatic or known AV malformations of the gastrointestinal tract.
- **[9.1]** Screening platelet count <75 x 10^9 cells/L.

Concomitant Conditions or Diseases

- **[10.2]** Active cancer (excluding non-melanoma skin cancer) defined as cancer not in remission or requiring active chemotherapy or adjunctive therapies such as immunotherapy or radiotherapy. Chronic hormonal therapy (eg, tamoxifen, anastrazole, leuprolide acetate) for cancer in remission is allowed.
- **[11.1]** Any medical condition (eg, atrial fibrillation) that requires use of any parenteral or oral anticoagulant(s) (eg, warfarin sodium or vitamin K antagonists, Factor II or Xa inhibitors, fibrinolytics) concomitantly with study medication.
- **[12.1]** Bilateral and unilateral above-knee lower extremity amputation.
- **[13]** Subject has known allergies, hypersensitivity, or intolerance to rivaroxaban or any of its excipients.
- **[14.1]** Severe renal insufficiency (baseline CrCl <30 mL/min calculated using the Cockcroft-Gault [6] formula provided in Section 9.1.2).
- **[15.1]** Known significant liver disease (eg, acute hepatitis, chronic active hepatitis, cirrhosis) which is associated with coagulopathy or moderate or severe hepatic impairment.
- **[16]** Known HIV infection.
- **[17]** Sustained uncontrolled systolic blood pressure (BP) of ≥180 mmHg or diastolic BP of ≥100 mmHg at randomization despite treatment.
- **[18.1]** Current drug or alcohol abuse, based on investigator's assessment.
- **[19.1]** Cardiogenic or septic shock with the need for vasopressor(s) or devices for blood pressure support during index hospitalization.
- **[20]** Presence of inferior vena caval filter
- **[21]** Severe bronchiectasis or cavitary tuberculosis or any other pulmonary condition (eg, vasculitis) at risk for major hemoptysis

Drugs or Procedures

- **[22.2]**

  a. Combined P-gp and strong CYP3A4 inhibitors (such as but not limited to ketoconazole, telithromycin or protease inhibitors) 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.

  b. 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.

- **[23.2]** Received fibrinolysis during index hospitalization, unless received for ischemic stroke at least 3 full days before randomization.
- **[24.2]** Use of antiplatelet therapy during the index hospitalization, including:

  a. ASA >162 mg/day

  b. Clopidogrel >75 mg/day or ticlopidine >250 mg twice daily

  c. Clopidogrel at any dose in combination with omeprazole or esomeprazole

  d. Dipyridamole >400 mg/day

  e. Cilostazol >200 mg/day

  f. Dual therapy with 2 or more antiplatelet agents (dipyridamole with ASA is permitted)

  g. Other G protein-coupled purinergic receptor P2Y (P2Y12) antagonists (eg, prasugrel, ticagrelor)

  h. Thrombin-receptor antagonists (eg, vorapaxar)
- **[25.1]** Childbearing potential without proper contraceptive measures, pregnancy or breast feeding.

  a. Before randomization, a woman must be either:

  - Not of childbearing potential: premenarchal; postmenopausal (>45 years of age with amenorrhea for at least 12 months or any age with amenorrhea for at least 6 months and a serum follicle stimulating hormone (FSH) level >40 IU/L]); permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral salpingectomy); or otherwise be incapable of pregnancy,
  - Of childbearing potential and practicing a highly effective method of birth control consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies: eg, established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device or intrauterine system; barrier methods: condom with spermicidal foam/gel/film/cream/suppository or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; male partner sterilization (the vasectomized partner should be the sole partner for that subject); true abstinence (when this is in line with the preferred and usual lifestyle of the subject).

    Note: If the childbearing potential changes after start of the study (eg, woman who is not heterosexually active becomes active, premenarchal woman experiences menarche) a woman must begin a highly effective method of birth control, as described above. The initiation of hormonal contraception for the purpose of the study is not recommended.

    A woman of childbearing potential must have a negative serum (β human chorionic gonadotropin [β hCG]) or urine pregnancy test at screening.

  b. A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a double-barrier method of birth control eg, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive

cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, and all men must also not donate sperm during the study, from the time of the first dose to the last dose of study drug.

- **[26]** Participation in another pharmacotherapeutic study or experimental medical device within 30 days before the start of study treatment.
- **[28.2]** Prescribed daily use of nonsteroidal anti-inflammatory agents (NSAIDs) during the index hospitalization
- **[29]** Subject is unwilling or unable to complete all study visits as well as follow-up visit.
- **[30]** Subject is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's status changes (including laboratory results or receipt of additional medical records) after screening but before randomization such that he or she no longer meets all eligibility criteria, the subject should not be randomized. But if the subject has been randomized, he/she should not be excluded from participation in the study and must be followed until the Day 75 (±5d) visit. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

Potential subjects 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 subjects require or take prohibited medications during the study as outlined below, they must either temporarily interrupt or permanently discontinue the study drug, as appropriate for the duration of the therapy with the prohibited medication:

Note: Numbered criteria in brackets are for data collection purposes and are intentionally non-sequential.

- **[2.2]** Combined P-gp and strong CYP3A4 inhibitors (such as but not limited to ketoconazole, telithromycin or protease inhibitors) 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.

- **[3.2]** 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.
- **[4.1]** Anticoagulant (eg, warfarin sodium or other vitamin K antagonists, Factor II or Xa inhibitors) is prohibited as concomitant therapy during the study. Study drug should be discontinued in subjects who develop any condition which requires anticoagulation or thromboprophylaxis (eg, atrial fibrillation, VTE) that will extend beyond the end of the study treatment phase.

- **[6.1]** Fibrinolytic therapy (see Section 10.2.1 for guidance)
- **[7.1]** Use of antiplatelet therapy, including:

  a. ASA >162 mg/day

  b. Clopidogrel > 75 mg/day or ticlopidine > 250 mg twice daily

  c. Clopidogrel at any dose in combination with omeprazole or esomeprazole

  d. Dipyridamole >400 mg/day

  e. Cilostazol >200 mg/day

  f. Dual therapy with 2 or more antiplatelet agents (dipyridamole with ASA is permitted)

  g. Other P2Y12 receptor antagonists (eg, prasugrel, ticagrelor)

  h. Thrombin-receptor antagonists (eg, vorapaxar)

  i. Prescribed daily non-steroidal anti-inflammatory drugs (temporary use as needed is allowed).
- **[9]** Modification of an effective pre-existing therapy should not be made for the explicit purpose of entering a subject into the study.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Subjects will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared before the study under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by subjects with CrCl ≥30 and <50 mL/min versus subjects with CrCl ≥50 mL/min and by country. Enrollment may be capped for subgroups with certain baseline characteristics (eg, index hospitalization duration, reason for index hospitalization, risk score, and index hospitalization thromboprophylaxis) or by country or region. 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.

The IWRS will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kits for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject.

Blinding

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

Data that may potentially unblind the treatment assignment (ie, events that contribute to the primary and secondary outcome or treatment allocation) 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.

Unblinding

Under normal circumstances, the blind should not be broken until all subjects have completed the study and the database is finalized. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be governed by knowledge of the treatment assignment of the subject. In such cases, the investigator may determine the treatment assignment or allocation by contacting the IWRS. 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, time, and reason for the unblinding must be documented by the IWRS in the source document. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner.

Subjects who have had their treatment assignment unblinded may continue on study drug unless the subject meets a study drug temporary interruption or permanent discontinuation criterion. Investigators should not disclose treatment assignment to the subject whenever possible.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. However, if an interim analysis is specified, the randomization codes and, if required, the translation of randomization codes into treatment and control groups will be disclosed to those authorized and only for those subjects included in the interim analysis.

If a subject has a suspected efficacy or bleeding outcome event during the study, the treating physician should exercise clinical judgment and follow established guidelines to apply the standard of care. Unblinding of study drug should not be necessary. Anticoagulation regimens do not require adjustment regardless of treatment group assigned when study drug is administered in the doses used in this study. There is no specific reversal agent for rivaroxaban; management of the subject with a bleeding event should not be impacted by knowledge of study drug treatment. If despite this guidance, the investigator believes it is in the best interest of the subject to unblind study drug, the investigator may determine the treatment assignment or allocation by contacting the IWRS as previously noted.

6. DOSAGE AND ADMINISTRATION

Treatment groups in this study are rivaroxaban and placebo. Subjects will be randomly assigned in a 1:1 ratio to receive rivaroxaban 10 mg daily (7.5mg daily in subjects with CrCl of ≥30 and

<50 mL/min) or matching placebo daily. Randomization will be stratified by subjects with CrCl ≥30 and <50 mL/min versus subjects with CrCl ≥50 mL/min and by country. The dose of study drug will not be adjusted in the event of change in CrCl between the 2 strata during the course of the study.

The first dose of study drug should be administered no later than the day after the subject leaves the hospital and as soon after randomization as possible. The date and time of the first dose of study drug and the last dose of LMWH or UFH should be recorded as accurately as possible. The first dose of study drug should not be delayed to allow administration under supervision. All subjects should take study drug (rivaroxaban or placebo) daily with or without food at approximately the same time each day, and discontinue study drug after they take a dose on Day 45. ***Regardless of the day on which the Day 45 Visit occurs, no study drug may be taken after Day 45.***

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 subject takes a dose of study drug on Day 45, the subject should discontinue study drug and complete the Day 45 (+4d) visit (refer to TIME AND EVENTS SCHEDULE). ***Regardless of the day on which the Day 45 Visit occurs, no study drug may be taken after Day 45***. Throughout the study, study drug will be dispensed at appropriate intervals (see the TIME AND EVENTS SCHEDULE) to ensure that subjects have adequate quantities of study drug between study visits. In addition, study site personnel will instruct subjects on how to store study drug for at-home use as indicated for this protocol. The storage recommendation for rivaroxaban or placebo is at room temperature (approximately 15° to 30°C).

Randomization in this study is preceded by a hospitalization for an acute illness and the study drug treatment phase extends for 45 days after randomization to correspond to the period of greatest risk for VTE. Chronic therapy with the study drug is not being tested. For these reasons, rivaroxaban will not be provided to the subject after the subject completes the Day 75 (±5d) visit, unless required by local regulations. It will only be after data from the entire study is analyzed that it will be determined if the population at risk will benefit from treatment.

Interruption of Study Drug

Study drug may be interrupted temporarily (see Section 10.2.1, Temporary Interruption of Study Treatment) as necessary for invasive procedures or as medically needed (eg, in the setting of a bleeding event or a required prohibited therapy). If a subject is hospitalized for any reason other than a VTE-related event or bleeding, study drug should be continued during hospitalization unless the treating physician feels that anticoagulation, temporary interruption or permanent discontinuation of study drug is clinically warranted. Subjects may be placed on appropriate anticoagulation at the discretion of the treating physician. In that case, study drug may be restarted upon discharge at the discretion of the investigator. These interruptions will be recorded on the electronic case report form (eCRF). For guidance on study drug temporary interruption, see Section 10.2.1.

Intentional stopping of study drug by the subject, unintentional stopping of study drug, or direction to temporarily interrupt study drug by the investigator or other physician will be documented. Study drug interruption will be recorded in the eCRF.

7. TREATMENT COMPLIANCE

The IWRS will keep track of study drug dispensed to the subjects. Subjects will return empty study drug containers and unused study drug at the Day 21 visit when a new supply of study drug is to be received. The last dose of study drug should be taken on Day 45. ***Regardless of the day on which the Day 45 Visit occurs, no study drug may be taken after Day 45***. Subjects will also return empty study drug containers and unused study drug at the Day 45 (+4d) visit.

Study drug accountability will be performed at the Day 21 and Day 45 visits. Subjects should report any unintentional interruption or missed doses to the study-site personnel at each visit. It is understood that subjects may occasionally miss a dose or that a subject may be placed on temporary interruption (see Section 10.2.1, Temporary Interruption of Study Treatment).

8. PRESTUDY AND CONCOMITANT THERAPY

For each subject, the drug identity and dose of the following relevant medications taken during the index hospitalization through the end of the study will be recorded on the appropriate page of the eCRF: antiplatelet (including NSAIDs) and anticoagulant medications, statins, and medications relevant to SAEs. Only the drug identity should be recorded for proton pump inhibitors, glucocorticoids, hormonal therapies including but not limited to estrogens, progesterones, androgens, anti-androgens and any analogues. In the event a prohibited medication other than NSAIDs is received, only the identity of the medication will be recorded.

Prophylactic treatment with LMWH or UFH during the index hospitalization must be reported as accurately as possible at screening.

Allowed Therapy

All decisions regarding concomitant medications are left to the treating physician unless otherwise required by the protocol.

Refer to Section 4.3 for prohibited therapies.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The TIME AND EVENTS SCHEDULE in the synopsis summarizes the frequency and timing of procedures applicable to this study.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

9.1.2. Screening Phase

Screening may begin any time after the admission for the index hospitalization, and once the informed consent is obtained.

Subjects with a modified IMPROVE VTE Risk Score of 2 or 3 must have had a local D-dimer value >2X ULN before randomization to be eligible for the study. For those subjects, if the D-dimer was not ordered as part of the standard of care by the treating physician during the index hospitalization, a screening sample may be obtained by site staff after obtaining informed consent. The informed consent may be a limited informed consent to allow for this screening activity. No other screening procedures must be performed until the full informed consent is obtained. Alternatively, the full study informed consent may be obtained if selected by site staff and necessary to be in compliance with local and IRB/Ethics Committee requirements.

For subjects enrolled with ischemic stroke as the reason for hospital admission and who received fibrinolysis agents as treatment for the stroke, a head CT or MRI must be obtained at least 24 hours after fibrinolysis. Results of the head CT/MRI must meet Inclusion Criterion [1.2] for the subject to be randomized.

Eligibility based on laboratory results will be determined using local laboratory results for the inclusion and exclusion clinical laboratory parameters, and the latest one will also serve as baseline if there are multiple laboratory values. Laboratory screening assessments that are part of the standard care performed by the investigator do not need to be repeated if performed within the time frame required by the protocol. A local D-dimer value should be obtained on all subjects; if available, a screening D-dimer value can be used if available. If more than 1 D-dimer value is available, the value obtained closest to the beginning of the index hospitalization should be used. Hemoglobin, platelet count and the serum creatinine utilized to determine randomization CrCL (calculated by IWRS using the Cockcroft-Gault formula) must be obtained at least as recently as 2 days before the subject leaves the hospital or later, but before randomization.

The creatinine clearance will be calculated by IWRS using the Cockcroft-Gault formula, which relates serum creatinine with age (in years) and body weight (in kg)[4,6]. If one measures creatinine concentration in mg/dL, then the following 2 equations are used for men and women:

$$\text{Men:} \quad \frac{[(140 - \text{age [yr]}) \times \text{weight (kg)}]}{[72 \times \text{creatinine (mg/dL)}]}$$

$$\text{Women:} \quad \frac{[(140 - \text{age [yr]}) \times \text{weight (kg)}]}{[72 \times \text{creatinine (mg/dL)}]} \times 0.85$$

If one measures creatinine concentration in µmol/L, then the following 2 equations are used for men and women:

$$\text{Men:} \quad \frac{[(140 - \text{age [yr]}) \times \text{weight (kg)}]}{[0.814 \times \text{creatinine (µmol/L)}]}$$

$$\text{Women:} \quad \frac{[(140 - \text{age [yr]}) \times \text{weight (kg)}]}{[0.814 \times \text{creatinine (µmol/L)}]} \times 0.85$$

All screening activities must be completed before randomization and the results must be available to the investigator for review to ensure that eligibility criteria are met.

9.1.3. Double-Blind Treatment Phase

Day 1/Day of Randomization

If the subject meets all of the inclusion and none of the exclusion criteria, he or she is eligible to be randomly assigned to receive rivaroxaban or placebo at the Day 1 visit.

Randomization should occur on the day the subject leaves the hospital; randomization will also be permitted the day after the subject leaves the hospital. Randomization may occur at the hospital, clinic or other discharge destination.

At the randomization visit, before randomization occurs, site staff must review the visit schedule and the importance of completing the study with both the subject and any family members present. Randomization should not occur if the subject:

- does not have transportation to study visits
- does not believe they will have sufficient support to comply with the protocol
- is being discharged to a destination other than home and acceptability of study participation has not been confirmed with the accepting physician
- post-discharge anticoagulation or thromboprophylaxis is planned

Also, before randomization occurs, site staff should review eligibility criteria, including concomitant medications administered during the index hospitalization and planned at discharge. Particular attention should be paid to ensure that acceptable types and doses of thromboprophylaxis were used during the index hospitalization, and that prohibited medications were not administered and are not planned.

After randomization, the first dose of study drug should be administered as soon as possible and no later than the day after the subject leaves the hospital. The time of the first dose should be recorded as accurately as possible. The first dose also should not be delayed to allow administration under supervision. The first dose does not need to be delayed because of the recent administration of LMWH or UFH. The administration date and time of the first dose of study drug will be recorded in the source document and eCRF. The subject will be instructed to take study drug daily through Day 45. ***Regardless of the day on which the Day 45 Visit occurs, no study drug may be taken after Day 45.***

Also, at the randomization visit, the importance of reporting signs and symptoms associated with bleeding, DVT and PE will be stressed. Subjects and family members, as appropriate, will be counseled and given educational material on the signs and symptoms associated with DVT, PE and bleeding.

For bleeding events, subjects and family members as appropriate, will be instructed:

- To seek medical attention if they develop bleeding
- To contact the investigative site staff or study investigator before the next dose of study medication is due
- To inform treating health care providers about study participation

Subjects and family members, as appropriate will also be instructed:

- About the subject's risk of DVT and PE
- About the signs and symptoms of DVT and PE
- To seek medical attention if they develop any of these signs or symptoms
- To contact the investigative site staff or study investigator as soon as symptoms develop and before the next dose of study medication is due
- To inform treating health care providers about study participation and their risk of DVT and PE.

The subject's family should be instructed to have a low threshold to contact the site and if necessary an unscheduled visit can be performed.

Treatment Visits

Subjects will be instructed to adhere to the visit schedule in the TIME AND EVENTS SCHEDULE. Treatment visits should be conducted at the site, but to allow for as complete follow up as possible, they may be conducted at home or at another discharge destination, if allowed by local regulatory and IRB/Ethics Committee requirements. Day 7 and Day 75 visits may be conducted as a telephone visit. Visits conducted at home may only be performed by medically qualified personnel (eg, training and education) as delegated by the Principal Investigator and as documented in the Delegation Log. If a visit in the subject's presence cannot be achieved, telephone contact with the subject should be attempted. If telephone contact with the subject cannot be achieved, the site should attempt to contact others who have knowledge of the subject as allowed by local and IRB/Ethics Committee requirements.

<u>Day 7 Visit</u>

The Day 7 Visit may be conducted at the clinic or other discharge destination including a home visit if allowed by local requirements or as a telephone visit. Visits conducted at home may only be performed by medically qualified personnel as delegated by the Principal Investigator and as documented in the Delegation Log.If the information is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. The visit window is -2 days/+5 days. Study personnel will confirm sufficient drug supply to allow for daily dosing through the Day 21 Visit, and will reinforce the dosing schedule and procedure to follow if a dose is missed. The clinical status review for suspected outcome events will be completed, as will the symptom assessment, consisting of a set of scripted questions

(Attachment 4). Adverse events will be collected as specified in Section 12, and concomitant medication will be collected as specified in Section 8.

Subject counseling provided at the randomization visit will be repeated in detail.

Day 21 Visit

The Day 21 Visit may be conducted at the clinic or other discharge destination including a home visit if allowed by local requirements. Visits conducted at home may only be performed by medically qualified personnel (eg, training and education) as delegated by the Principal Investigator and as documented in the Delegation Log. The Day 21 Visit should not be conducted as a telephone visit. Attendance in person is required to allow study drug dispensing. The visit window is -3 days/+7 days to ensure compliance. Study drug accountability will be performed and a supply of 30 tablets dispensed. Site staff will reinforce the dosing schedule and procedure to follow if a dose is missed. The clinical status review for suspected outcome events will be completed, as will the symptom assessment, consisting of a set of scripted questions (Attachment 4) and a clinical assessment. Adverse events will be collected as specified in Section 12, and concomitant medication will be collected as specified in Section 8.

Subject counseling provided at the randomization and Day 7 Visits will be again repeated in detail.

Day 45 Visit

The Day 45 Visit may be conducted at the clinic or other discharge destination including a home visit if allowed by local requirements. Visits conducted at home may only be performed by medically qualified personnel (eg, training and education) as delegated by the Principal Investigator and as documented in the Delegation Log. The Day 45 Visit should not be conducted as a telephone visit. The visit window is -0 days/+4 days to ensure all events through the end of treatment are captured. The last dose of study drug will be administered on Day 45 regardless of the day of the Day 45 visit. ***Regardless of the day on which the Day 45 Visit occurs, no study drug may be taken after Day 45.*** Study drug accountability will be performed. The clinical status review for suspected outcome events will be completed, as will the symptom assessment, consisting of a set of scripted questions (Attachment 4) and a clinical assessment. Adverse events will be collected as specified in Section 12, and concomitant medication will be collected as specified in Section 8.

Subject counseling provided at the randomization, Day 7, and Day 21 Visits will be again repeated in detail.

Unscheduled Visit

Subjects may be seen by the investigator between scheduled visits for any reason such as:

- Suspected efficacy or bleeding outcome event
- Early study drug permanent discontinuation
- Adverse event, based upon the severity and clinical judgment of the investigator
- Lost medication requiring replacement

Early Study Drug Permanent Discontinuation/Early Withdrawal from Study

If the subject permanently discontinues study drug before Day 45, he/she should be instructed to complete an unscheduled visit and the remaining scheduled visits, including the Day 7 (-2d/+5 d) and Day 21 (-3d/+7d) visits and the Day 45 (+4d) and Day 75 (±5d) visits (see TIME AND EVENTS SCHEDULE). Because the primary efficacy analysis of the study is based upon the intention-to-treat (ITT) principle, the investigator should inform the subject of the importance of returning for all study visits. It is imperative for the integrity of the trial and results to have vital status and other outcomes ascertainment. If the subject is unwilling or unable to return for any visits, the site should collect as much follow-up information as possible, including contacting the subject or legally acceptable representative by telephone or by mail to determine vital status and if an outcome has occurred, as agreed to by the subject during the initial informed consent process. If applicable, vital status and other outcomes should be obtained by reviewing the subject's medical or public records unless this contact is not allowed by local regulations.

If the subject withdraws consent from the study, this must be documented in the source document and the subject will be asked to supplement the withdrawal of consent with a signed written statement documenting refusal for all subsequent contact.

9.1.4. Post-treatment Phase (Follow-Up)

Day 75 Visit

The Day 75 Visit may be conducted at the clinic or other discharge destination including a home visit if allowed by local and IRB/Ethics Committee requirements or by a telephone visit. Visits conducted at home may only be performed by medically qualified personnel (eg, training and education) as delegated by the Principal Investigator and as documented in the Delegation Log. The visit window is -5 days/+5 days. The clinical status review for suspected outcome events will be completed, as will the symptom assessment, consisting of a set of scripted questions (Attachment 4). Adverse events will be collected as specified in Section 12, and concomitant medication will be collected as specified in Section 8.

If the information is obtained via telephone contact, written documentation of the communication must be available for review in the source documents.

Randomization in this study is preceded by a hospitalization for an acute illness and the study drug treatment phase extends for 45 days after randomization to correspond to the period of greatest risk for VTE. Chronic therapy with the study drug is not being tested. For these reasons, rivaroxaban will not be provided to the subject after the subject completes the Day 75 (±5d) visit unless required by local regulations. It will only be after data from the entire study is analyzed that the sponsor will determine if the population at risk will benefit from treatment.

9.2. Efficacy Evaluations and Outcomes

As described in Section 1.1.5, PE is reported by physicians to be the most commonly missed or delayed diagnosis. As MARINER is a symptomatic event-driven trial it is critical all efficacy outcome events, including symptomatic PE are appropriately diagnosed. Any suspected event that includes symptoms or signs suggestive of a PE must be sent for adjudication. Investigators are encouraged to give careful consideration of the diagnosis of PE for subjects admitted under their care with symptoms of or exacerbations of conditions such as (pneumonia, bronchitis, heart failure, cardiorespiratory failure and exacerbation of COPD). Investigators are also strongly encouraged to expeditiously contact the treating physician for any subject hospitalized with any of these conditions.[2,32,12]

9.2.1. Efficacy Evaluations, Outcomes and Adjudication

This is a clinical outcomes study. The primary efficacy outcome is the composite of all symptomatic VTE events (lower extremity DVT and non-fatal PE) and VTE-related death (death due to PE or death in which PE cannot be ruled out as the cause).

Secondary efficacy outcomes are:

- VTE-related death (death due to PE or death in which PE cannot be ruled out as the cause)
- Symptomatic VTE (lower extremity DVT and non-fatal PE)
- The composite of symptomatic VTE (lower extremity DVT and non-fatal PE) and ACM
- The composite of symptomatic VTE (lower extremity DVT and non-fatal PE), MI, non-hemorrhagic stroke and CV death (death due to a known CV cause and death in which a CV cause cannot be ruled out; by this definition, a VTE-related death is considered a CV death)
- ACM

Exploratory efficacy outcomes are:

- Symptomatic lower extremity DVT
- Symptomatic non-fatal PE
- Symptomatic upper extremity DVT
- MI
- Non-hemorrhagic stroke

- Re-hospitalization for symptomatic VTE (lower extremity DVT and non-fatal PE) within 30 days after randomization

Submission of a suspected event for adjudication will be required for:

- All deaths
- Suspected events that include symptoms or signs suggestive of PE or DVT.
- Performance of any imaging or other diagnostic study that could yield an incidental diagnosis of PE or DVT.
- Suspected events that include acute coronary syndrome or MI. Chest pain determined not to be cardiac in origin does not need to be sent for adjudication.
- Suspected events that include symptoms compatible with a TIA or stroke. Events determined not to be a TIA or stroke (eg, seizure, hypoglycemia) do not need to be sent for adjudication.

Any clinical event that suggests the possibility that an efficacy outcome event has occurred (including ACS and TIA) should be indicated on the Clinical Status page of the eCRF and will be sent for adjudication. Examples of objective testing diagnostic procedures that may have been performed as part of the standard of care are listed in Attachment 2. For imaging studies, a copy of the original study should be sent with the adjudication package. For other tests, a report of the results will suffice. All clinical data must be sent to CEC for adjudication. The CEC may request additional imaging in order to ensure appropriate adjudication. The CEC will apply the definitions (see Attachment 1) contained in the CEC charter to adjudicate and classify the events while blinded to treatment assignment. Adjudicated results will be used for final analyses.

9.2.2. Approach to the Subject with an Efficacy Outcome Event

If a subject has a suspected efficacy outcome event during the study, the treating physician should exercise clinical judgment and follow established guidelines to apply the standard of care. At the treating physician's discretion, the routine measures described below may be considered.

- Temporarily interrupt or permanently discontinue study drug treatment as clinically indicated. Unblinding of study drug should not be necessary, as anticoagulation regimens do not require adjustment regardless of treatment group assigned when study drug is administered in the doses used in this study.
- Perform necessary diagnostic procedures and consider the usual treatment measures for VTE and/or cardiac ischemic events if physical examination and diagnostic testing suggest benefit could be obtained.

After clinical evaluation of the suspected efficacy outcome event is completed restarting study drug may be considered if none of the conditions requiring permanent discontinuation are present (Section 10.2.3, Permanent Discontinuation of Study Treatment), and after consultation with the medical monitor. In the event that a decision is made to restart study drug (Section 10.2.1, Temporary Interruption of Study Treatment), guidelines for restarting study drug

(Section 10.2.2, Approach to Subjects with Temporary Interruption of Study Treatment) may be followed if applicable based on the clinical judgment of the investigator.

9.3. Pharmacokinetics

9.3.1. Evaluations

Pharmacokinetic samples will be collected at selected countries and sites that can provide the logistical requirements necessary for the PK sampling. Fasting is not required to validate the population PK model. Four sparse blood samples will be collected at 2 visits for about 600 subjects (300 subjects in rivaroxaban subjects [200 subjects in the 10 mg daily and 100 in the 7.5 mg daily group] and 300 in the placebo group) (Table 3 and Table 4). These data will be used to describe drug exposure. Blood samples (2.0 mL each) for determination of rivaroxaban plasma concentrations will be collected at the time points indicated in the TIME AND EVENTS SCHEDULE. The exact date and time of the administration of the current dose (plus the 2 preceding doses) and the precise actual time of blood sample collection must be accurately documented in the eCRF or laboratory requisition form, as appropriate. The PK sub-study will only be conducted at specific sites (ie, those that have the capability to draw, process, and store the PK samples), where all subjects screened will be given the choice to participate. For the PK sample population, drug should always be taken in the morning. At the Day 7 visit, the study drug must be administered under supervision following the collection of the trough sample. At the Day 21 visit, subjects will take the study medication at home in the morning and visit the clinic for PK sampling. At the Day 21 visit, the date and time of the dose administration must be recorded and there needs to be a minimum of 3 hours between sample collections. Subjects may be confined to the study site during PK sampling, if considered appropriate. Samples will be used to evaluate the PKs of rivaroxaban (Attachment 3).

Table 3 Pharmacokinetic Suggested Sampling Schedule

	Day 7		Day 21	
PK Blood sampling (selected sites and subjects)	Pre-dose	Hours Post-dose	Hours Post-dose	
		1-4 Hours	3-7 Hours	7-12 Hours
	X	X	X	X

Table 4: Summary of PK Suggested Observations for Rivaroxaban Arm

Active doses (mg/day)	Total number of subjects with measured samples on Rivaroxaban	Number of Measurements Plasma Concentrations
7.5	100	400
10	200	800
Total	300	1,200

9.3.2. Analytical Procedures

Pharmacokinetics

Plasma samples will be analyzed to determine concentrations of rivaroxaban using a validated, specific and sensitive liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) method.

9.3.3. Pharmacokinetic Parameters

Based on the individual plasma concentration-time data, using the actual dose taken and the actual sampling times, PK parameters and exposure information of rivaroxaban will be derived using population PK modelling. Baseline covariates (eg, lean body mass, age, serum creatinine) will be included in the model.

9.4. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data collection will include re-hospitalization (including ER visits, intensive care unit and cardiac care unit stays), length of stay and subject discharge destination (after re-hospitalization).

9.5. Safety Evaluations and Outcomes

9.5.1. Bleeding Events

The study will include the following evaluations of safety and tolerability according to the time points provided in the TIME AND EVENTS SCHEDULE: ISTH major bleeding, non-major clinically relevant bleeding, other bleeding, adverse events, and clinical laboratory tests.

The study will use the ISTH Bleeding Event Classification Scale to assess bleeding events as major, non-major clinically relevant bleeding, or other bleeding. Similar to efficacy outcomes, the same independent CEC will adjudicate and classify bleeding events according to definitions in the CEC charter. The CEC will also classify bleeding events using the Bleeding Academic Research Consortium scale as a supportive approach.[27]

The principal safety outcome for this study is major bleeding using validated ISTH bleeding criteria. Other safety outcomes are non-major clinically relevant bleeding and other bleeding.

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

Non-major 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 treatment, or associated with discomfort for the subject such as pain or impairment of activities of daily life.

Examples of non-major 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, etc.)
- 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, or
- Intramuscular hematoma
- Subcutaneous hematoma if the size is larger than 25 cm^2 or larger than 100 cm^2 if provoked
- Multiple source bleeding

Other bleeding is defined as any other overt bleeding episodes that do not meet the ISTH criteria for major or non-major clinically relevant bleeding.

Details of all bleeding events will be captured in the eCRF.

All suspected bleeding events will be submitted for adjudication.

9.5.2. Approach to the Subject with a Bleeding Event

If a subject has a serious bleeding event during study drug treatment, the following routine measures should be considered:

- Delay the next study drug administration, or discontinue treatment if indicated. Rivaroxaban has a plasma half-life of approximately 5 to 9 hours, and in some subjects up to 13 hours. Therefore, temporary cessation of study drug may allow control of bleeding. Unblinding of study drug should not be necessary. As there is not a specific reversal agent for rivaroxaban, management of the subject should not be impacted by knowledge of study drug treatment.
- 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 (i.e., rule out disseminated intravascular coagulation,

thrombocytopenia, and other coagulopathies; kidney and liver dysfunction; concomitant medications, etc.), 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).[43]

- Activated prothrombin complex concentrate
- Prothrombin complex concentrate
- Recombinant factor VIIa (NovoSeven®)

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

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 drug may be considered based on the clinical judgment of the investigator.

9.5.3. Other Safety Assessments

Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

Clinical Laboratory Tests

Separate laboratory screening tests are not expected to be performed by the investigator as these will likely be part of the subjects' hospital evaluation. No pre-specified laboratory tests will be performed for the duration of the study. However, these subjects are likely to have local laboratory tests performed during their index hospitalization. Any laboratory test along with reference ranges relevant to a serious adverse event or an outcome event should be recorded on the appropriate eCRF page.

The following tests results with reference ranges will be obtained from the hospital laboratory/local laboratory at the time of the index hospitalization:

- hematology
  - hemoglobin
  - platelet count
- serum creatinine (CrCl to be calculated by IWRS using Cockcroft-Gault formula[6])
- D-dimer
- serum or urine pregnancy testing for women of childbearing potential only

9.6. Benefit-Risk Balance

Benefit-risk balance of rivaroxaban will be explored. Refer to Section 11.8, Benefit-Risk Analysis for details.

9.7. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. If blood samples are collected via an indwelling cannula, an appropriate amount (1 mL) of fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. After blood sample collection, the cannula should be managed per local practice.

Refer to the TIME AND EVENTS SCHEDULE for the timing and frequency of all sample collections.

10. SUBJECT COMPLETION/WITHDRAWAL

10.1. Completion

The total duration for a subject who completes the study after randomization is expected to be 75 days.

All feasible efforts and measures will be made to collect complete vital status and other outcome data from randomization to the Day 75 (±5d) visit for each subject randomized in this study, regardless of compliance with study drug or visits. For subjects who are lost to follow-up or withdraw consent from the study, efforts will be made to obtain their vital status and other outcomes from permitted sources.

It is important to note that withdrawal of consent does not withdraw permission to collect vital status and other outcomes. Withdrawal of permission to collect vital status and other outcomes must be made separately. In cases where subjects indicate they do not want to "continue", investigators must determine whether this refers to discontinuation of study treatment (the most common expected scenario), unwillingness to attend follow-up visits, unwillingness to have telephone contact, unwillingness to have any contact with study personnel, or unwillingness to allow contact with a third party (eg, family member, doctor). In all cases, every effort must be made to continue to follow the subject, and vital status and other outcomes must be determined for all randomized subjects.

10.2. Discontinuation of Study Treatment

If a subject's study treatment must be discontinued before the end of the double-blind treatment phase, the subject must continue to be followed for efficacy and safety outcomes.

During the study, should the subject develop any condition, which in the investigator's judgment requires long-term anticoagulation thromboprophylaxis, or fibrinolysis, the subject will have study treatment either temporarily interrupted or permanently discontinued and will be managed as deemed appropriate by the treating physician. The subject will be asked to continue in the study to be followed for efficacy and safety outcomes.

10.2.1. Temporary Interruption of Study Treatment

If the subject requires re-hospitalization (re-hospitalization is defined as a combined total of inpatient and/or ER stay ≥24 hours) during the study drug treatment for reasons other than the primary efficacy outcome or bleeding, the subject should be maintained on the study drug at the discretion of the investigator. If the treating physician feels that the subject requires any anticoagulation during the re-hospitalization, study drug needs to be temporarily interrupted, and can be resumed upon hospital discharge. Mechanical methods of prophylaxis may be used during hospitalization. If this method is chosen, study drug may be continued.

In addition, the study drug should be temporarily interrupted if the subject:

- Develops any medical condition that may require use of anticoagulant therapy, thromboprophylaxis, fibrinolysis or poses an increased bleeding risk.
- Undergoes percutaneous coronary intervention, coronary artery bypass graft, any other interventional procedure, that may require use of anticoagulant therapy, thromboprophylaxis, or poses an increased bleeding risk. For temporary interruption of study drug for an elective procedure or surgery, it is suggested that investigators follow measures in Table 4 and Table 5 (Section 10.2.2 Approach to Subjects with Temporary Interruption of Study Treatment).
- Experiences a major bleeding event other than intracranial bleeding. For less severe bleeding events, investigator discretion is allowed. If possible, study drug should be resumed when the bleeding event has resolved and the cause has been identified and corrected.
- If a subject develops a new neurologic deficit or significant alteration in mental status suggesting a cerebral vascular accident. Once a diagnosis is definitively made and appropriate treatment is provided, the study drug may be restarted at the discretion of the investigator.
- Develops a platelet count less than 50,000/µL. If a repeat platelet count is obtained, and the result indicates that the abnormal platelet count was spurious, study drug may be restarted. If the finding was not spurious, study drug may be restarted after 2 consecutive values greater than 75,000/µL at least 1 week apart have been obtained.
- Has a serious adverse event that is considered by the investigator to be possibly related to, or exacerbated by, study drug administration.
- Requires a prohibited therapy on a temporary basis (see Section 8, Prestudy and Concomitant Therapy).

10.2.2. Approach to Subjects with Temporary Interruption of Study Treatment

If study drug is temporarily interrupted to allow a procedure to be performed, the routine measures described in Table 5 and Table 6 should be considered:

Table 5: Preoperative Interruption of Rivaroxaban: A Suggested Management Approach (adapted from Spyropoulos and Douketis 2012)

Patient Renal Function	Low Bleeding Risk Surgery[a] (2-3 drug half-lives between last	High Bleeding Risk Surgery[b] (4-5 drug half-lives between last

	dose and surgery)	dose and surgery)
Normal or mild impairment (CrCl ≥50 mL/min), or moderate (CrCl ≥30 and <50 mL/min) impairment	*Last dose*: 2 days before surgery (skip 1 dose)	*Last dose*: 3 days before surgery (skip 2 doses)

CrCl, creatinine clearance.
[a] aiming for mild-to-moderate residual anticoagulant effect at surgery (<12-25%).
[b] aiming for no or minimal residual anticoagulant effect (<3-6%) at surgery.

Table 6: **Postoperative Resumption of Rivaroxaban: A Suggested Management Approach**

Low Bleeding Risk Surgery	High Bleeding Risk Surgery
resume on evening of or day after surgery (within 24 hours postoperative)	resume 2 to 3 days after surgery (within 48 to 72 hours postoperative)

Spyropoulos, 2012[38].

10.2.3. Permanent Discontinuation of Study Treatment

If a subject must be permanently discontinued from study drug before the end of the double-blind treatment phase, this will not result in automatic withdrawal of the subject from the study, and the subject should continue to be followed for efficacy and safety outcomes (for details see Section 3.1).

A subject should be permanently discontinued from study drug if:

- The investigator believes that for safety reasons (ie, adverse event) it is in the best interest of the subject to stop study drug.
- The subject develops any condition which requires anticoagulation or thromboprophylaxis extending beyond the treatment phase of the study (eg, atrial fibrillation, VTE).
- The subject becomes pregnant.
- The subject has a fall in CrCl to below 20 mL/min or 2 consecutive measurements less than 30 mL/min at least 1 week apart (as calculated by Cockcroft-Gault formula, see Section 9.1.2) during the study.
- The subject requires hemofiltration or dialysis on a permanent basis
- The subject requests to discontinue study drug permanently
- The subject has a hemorrhagic stroke, or intracranial bleeding

If the subject permanently discontinues study drug before Day 45, he/she should be instructed to complete an unscheduled visit and the remaining scheduled visits, including the Day 7 and Day 21 visits (if not yet completed), and Day 45 (+4d) and Day 75 (±5d) visits (Section 9.1.3). The Day 45 visit should be a clinic visit; the Day 75 visit may be a telephone visit.

The eCRF is to be completed to identify the reason for permanent discontinuation of study drug. The investigator will provide a narrative to describe any adverse events that occur up to the Day 75 (±5d) visit. The appropriate adverse event or serious adverse event sections of the eCRF

are to be completed. If study drug is terminated for a serious adverse event, expedited reporting (within 24 hours) is also required as outlined in Section 12.3.2, Serious Adverse Events.

10.3. Withdrawal From the Study

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

- Lost to follow-up (only after all means of all subsequent contact, including locator services where permitted by law, up until the Day 75 (±5d) visit, have been exhausted, lost to follow-up will be declared).
- Withdrawal of consent (unless specifically refused by the subject, subject contact will be made to obtain vital status and other outcomes at the Day 75 (±5d) visit).

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced.

If a subject withdraws consent from study or is lost to follow-up, his or her vital status and other outcomes will be collected at the Day 75 (±5d) visit either by telephone or in person, or if applicable, by a review of the subject's medical or public records unless this contact is not allowed by local regulations.

11. STATISTICAL METHODS

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 of the study drug is outlined below. A more detailed SAP, including detailed censoring rules for time to event analyses and imputation rules for missing or partially missing dates, will be provided in a separate document that will be finalized before the first subject is randomized.

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 CIs at a nominal 2-sided level of 95%.

Adjudicated results on efficacy and safety outcomes will be used for the interim and final analyses.

11.1. Analysis Set and Analysis Phase

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

11.1.1. Analysis Sets

- Intention-to-Treat (ITT) (as in the International Conference on Harmonisation [ICH] E9 guideline): This analysis set consists of all randomized subjects who have a signed valid informed consent.
- Per-Protocol (PP): This analysis set is a subset of the ITT analysis set. Subjects with key protocol deviations will be excluded from the PP analysis set. Key protocol deviations will be defined in the SAP.
- Safety: This analysis set is a subset of the ITT analysis set, consisting of subjects who receive at least 1 dose of study drug.

11.1.2. Analysis Phases

- Up-to-Day-45: This analysis phase includes all data from randomization to Day 45 (inclusive).
- On-Treatment: This analysis phase includes all data from randomization to 2 days after the last dose of the study drug (inclusive).

11.2. Sample Size Determination

This is an event-driven study. The targeted total number of primary efficacy outcome is 161, based on the ITT analysis set and Up-to-Day-45 analysis phase. If a subject has multiple events, only the first is counted towards study size determination.

This targeted total number of events is determined using statistical software East 5.3 based on the primary efficacy analysis (defined later) and the following assumptions:

- 40% relative risk reduction (RRR) in the primary efficacy outcome based on the ITT analysis set and Up-to-Day-45 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 161 events, it is estimated that a total of approximately 8,000 subjects 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 2.5%. In the event that the actual observed blinded pooled event rate is lower than the assumed rate, more subjects may be enrolled to accumulate additional outcome events. Randomization in this study may be stopped at approximately 12,000 subjects for administrative considerations even if the targeted 161 events have not been observed by then. The total number of VTE-related death events may also be taken into account when deciding to stop randomization.

The above assumptions are based on observations from the MAGELLaN study and the IMPROVE VTE risk score published data.[10, 11, 31, 25, 26, 37]

Table 7 below additionally shows the approximate numbers of randomized subjects needed to observe 161 events based on several other placebo incidence rates.

Table 7: Approximate Number of Subjects Needed to Observe 161 Events

Placebo Incidence Rate	Number of Subjects
3.0%	6,700
2.75%	7,300
2.5%	8,000
2.25%	9,000
2.0%	10,100

11.3. Efficacy Analyses

Primary Efficacy Outcome

The primary efficacy outcome will be analyzed based on the time from randomization to the first occurrence of symptomatic VTE (lower extremity DVT and non-fatal PE) and VTE-related death (death due to PE or death in which PE cannot be ruled out as the cause) in the ITT analysis set and Up-to-Day-45 analysis phase. The primary statistical alternative hypothesis is that rivaroxaban is superior to placebo on the primary efficacy outcome, that is, time to event for the rivaroxaban group is stochastically later than that for the placebo group from randomization up to Day 45. 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 HR of rivaroxaban versus placebo is less than 1, and the null hypothesis is that the HR is at least 1.

The primary statistical hypothesis will be tested using Cox proportional hazards model, stratified by subjects with CrCl ≥30 mL/min and <50 mL/min versus subjects with CrCl ≥50 mL/min, with the treatment (as randomized) as the only covariate. This primary efficacy analysis will be based on the ITT analysis set and Up-to-Day 45 analysis phase. Subjects will be analyzed according to the treatment group to which they are randomized, regardless of actual treatment received. As an operational arrangement, the 2-sided p-value will be reported, and if it is less than the 2-sided alpha of 0.05, then superiority of the study drug will be declared when the observed survival

functions favor rivaroxaban. Note that the above testing procedure is equivalent to stratified logrank test[40]. The use of the Cox model format facilitates a consistent presentation of tests and CIs from analyses of efficacy and safety outcomes and from subgroup and sensitivity analyses.

The point estimate and corresponding 95% CI for the HR (rivaroxaban to placebo) will be provided based on the 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 adding a treatment by logarithm-transformed time interaction into the Cox model. If there is strong indication that the proportional hazards assumption is not valid, the 95% CI for relative risk of rivaroxaban versus placebo based on the incidence of the primary efficacy outcome from randomization up to Day 45 will be additionally provided, using the Cochran–Mantel–Haenszel (CMH) statistic with stratification by CrCl groups.

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

The following sensitivity analyses of the primary efficacy outcome will be conducted to assess the robustness of the conclusion from primary efficacy analysis: a) stratified Cox model as in the primary efficacy analysis but additionally stratified by region, b) stratified Cox model as in the primary efficacy analysis but based on the per-protocol analysis set and on-treatment analysis phase. Additional post-hoc analyses may be conducted to investigate unexpected results. Off-treatment primary efficacy outcome events will be summarized by treatment groups.

As described in Sections 9 and 10, extensive efforts will be made to collect complete vital status and other outcome data for all subjects randomized in this study. The amount of unavoidable missing follow-up in this study with relatively short treatment duration of 45 days is not expected to influence the conclusion from the efficacy analyses. To illustrate the extent of missingness, the numbers of subjects with missing follow-up and the percentages of missing follow-up time out of supposed follow-up time will be summarized. Sensitivity analyses will be conducted to estimate any additional events from the rivaroxaban and placebo group during the missing follow-up time that are needed to overturn a superiority conclusion from the primary efficacy analysis. Additional details will be provided in the SAP.

Homogeneity of treatment effects, both in HR and direction in the following subgroups will be assessed by subgroup analysis. Analysis methods and any changes to these subgroups will be detailed in the SAP.

- Age (< 65 vs ≥65; <75 vs ≥75 years)
- Sex (men vs women)
- Race (White vs others)
- Geographic region (North America, South America, Western Europe, Eastern Europe, other)
- CrCl (≥30 to <50, ≥50 to <80, ≥80 mL/min)

- Body Mass Index (<25, ≥25 to <35, ≥35 kg/m^2)
- Admitting diagnosis (HF with reduced ejection fraction, acute respiratory insufficiency or acute exacerbation of COPD, acute ischemic stroke, acute infectious disease, and inflammatory diseases)
- History of diabetes (yes vs no)
- History of cancer (yes vs no)
- Baseline D-dimer level
- Baseline aspirin use (yes vs no)
- Baseline thienopyridine use (yes vs no)
- Baseline proton pump inhibitor use (yes vs no)
- Duration of index hospitalization (3 to 6, 7 to 10 days)
- Duration of anticoagulation during index hospitalization (3 to 6, 7 to 10 days)
- LMWH or UFH during index hospitalization (LMWH vs UFH)
- Total modified IMPROVE VTE risk factor score (2, 3, ≥4)

Secondary Efficacy Outcomes

Each secondary outcome will be analyzed based on time from randomization to the first occurrence in the ITT analysis set, and the Up-to-Day-45 analysis phase. The same stratified Cox model as that for the primary efficacy outcome will be used. Details will be provided in the SAP.

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 sequentially using a closed testing procedure in the following hierarchical order, each at alpha of 0.05 (2-sided):

- VTE-related death (death due to PE or death in which PE cannot be ruled out as the cause)
- Symptomatic VTE (lower extremity DVT and non-fatal PE)
- The composite of symptomatic VTE and ACM
- The composite of symptomatic VTE (lower extremity DVT and non-fatal PE), MI, non-hemorrhagic stroke and CV death (death due to a known CV cause and death in which a CV cause cannot be ruled out; by this definition, a VTE-related death is considered a CV death)
- ACM

Exploratory Efficacy Outcomes

Each exploratory outcome will be summarized by treatment groups based on the ITT analysis set and Up-to-Day-45 analysis phase.

11.4. Pharmacokinetic Analyses

The population PK model will characterize and predict the overall exposure to rivaroxaban and determine different PK parameters, such as, clearance (CL/F), volume of distribution (V/F), first-order absorption rate constant (Ka), area under the plasma concentration curve (AUC), maximum serum concentration (C_{max}), minimum serum concentration (C_{min}), time to reach maximum concentration in plasma (t_{max}), and half-life ($t_{1/2}$).

A previously developed population PK model will be used in an attempt to externally validate it using data from the current study (ODIXa-DVT, 2006; EINSTEIN-DVT, 2006; BAY 59-7939 /12143, 2008). The model will be utilized to predict the PK parameters for the current medically ill population and to generate empirical Bayesian (individual) predictions for all concentrations in the current data set. Predictive performance check of the model will be analyzed. Changes to the structural components of the model will be performed to address any observed model misspecifications.

11.5. Medical Resource Utilization and Health Economics Analyses

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

11.6. Safety Analyses

Bleeding Outcomes

The principal safety outcome will be analyzed based on time from randomization to the first occurrence of ISTH major 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. Subjects will be analyzed according to study drug received. If a subject inadvertently receives both drugs, the subject will be analyzed as randomized.

Non-major clinically relevant bleeding and the composite of major plus non-major clinically relevant bleeding will be analyzed based on time from randomization to the first occurrence. The same analysis as that for the principal safety outcome will be used. Bleeding Academic Research Consortium bleeding event classification categories will be analyzed similarly.

All bleeding, other bleeding, as well as sub-categories of major bleeding, including critical sites, will be also summarized by treatment groups.

Adverse Events

For adverse events that are collected as specified in Section 12, ADVERSE EVENT REPORTING, the verbatim terms reported in the eCRF by investigators to identify adverse events will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA). For each MedDRA preferred term, the percentage of subjects who report at least 1 occurrence of the given event will be summarized by treatment group. Additional summaries, listings, or subject narratives may be provided, as appropriate.

Clinical Laboratory Tests

Because this study will not collect laboratory data routinely, laboratory data will not be summarized. Local lab data may be discussed in subject narratives.

Vital Signs

Descriptive statistics of pulse and blood pressure will be provided.

Physical Examination

Descriptive statistics of physical examination findings will be provided.

11.7. Interim Analysis

An interim analysis for futility will be conducted when approximately 50% of subjects with adjudicated primary efficacy outcome events have been observed (about 50% of the expected total number of events based on the actual observed blinded pooled event rate even if this event rate is lower than the assumed rate) and there will be no alpha adjustment to the final analysis. The IDMC will review results of the planned interim analysis and make a recommendation whether the study should be continued as planned, modified, or terminated prematurely due to futility or safety.

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. Detailed characteristics of non-binding futility criteria will be specified in the SAP.

11.8. Benefit-Risk Analysis

The benefit-risk of rivaroxaban vs 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 patients). 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 (lower extremity DVT and non-fatal PE) and VTE-related death (death due to PE and death in which PE cannot be ruled out as the cause) up to Day 45 post-hospital discharge) and the principal safety outcome (the ISTH major bleeding). This analysis phase includes all data from randomization to Day 45 (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, eg, in the context of irreversible harm. The Kaplan-Meier method will be used to display and evaluate the benefits and risks over time. Also a bivariate approach to benefit-risk assessment will be explored.[21] Additional details for benefit-risk analysis will be specified in the SAP.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Rivaroxaban has been extensively studied in Phase 1 through Phase 4 clinical studies involving more than 70,000 patients and its overall adverse event profile has been well described. Appropriate information concerning adverse events were systematically collected and submitted to regulatory authorities. For the purposes of this study (and after discussion with appropriate regulatory agencies) a value-driven approach to safety data collection will be utilized. Certain non-serious adverse events will not be collected, while certain events will be collected as suspected outcome events and therefore not reported as serious adverse events. All data on safety and outcomes will be reviewed regularly by an unblinded IDMC.

Section 12.1.1 describes the usual definitions of adverse events and serious adverse events.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. 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)

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and EU 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 subject 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 or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- 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 subject 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 will not be considered as adverse events or serious adverse events (See Section 12.3.1, All Adverse Events).

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 Investigator's Brochure[19].

Adverse Event Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2.

12.1.2. Attribution Definitions

Not Related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. 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 subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

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

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Inadvertent or accidental exposure to a sponsor study drug
- Any failure of expected pharmacologic action (ie, lack of effect) of a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, 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.

12.3. Procedures

12.3.1. All Adverse Events

In this study, recording of only a subset of adverse events is necessary. However, any adverse event of particular concern to the investigator may be recorded in the eCRF to alert the sponsor.

The following are excluded from adverse event collection and reporting, regardless of seriousness or severity. Exempted events will be captured on the eCRF as suspected outcome events only and will be waived from unblinding and exempted from expedited reporting and include:

- VTE-related death (death due to PE or death in which PE cannot be ruled out as the cause)
- MI
- ACS
- Stroke
- TIA
- Symptomatic VTE (lower or upper extremity DVT and PE)
- Bleeding events

If the CEC determines that a suspected event does not meet the criteria for an outcome event as defined in the CEC charter, it will still be excluded from adverse event collection and reporting even if serious criteria were met.

Serious Adverse Events

All serious adverse events that are not outcome events as listed above should be reported to the sponsor as described in Section 12.3.2. While one of the efficacy outcome measures is ACM, any non-VTE-related death will be reported to the sponsor as a serious adverse event.

Certain adverse events are considered to be Adverse Events of Special Interest and should be reported as serious adverse events. These include:

- Suspected severe toxic effect on the bone marrow, such as severe thrombocytopenia (platelet count less than 50,000/µL), severe neutropenia (white blood cell count less than 500/µL), pancytopenia, aplastic anemia
- Suspected severe hypersensitivity reaction (eg, anaphylaxis, angioedema, severe urticaria, bronchospasm, etc.)
- Severe skin reactions such as Stevens-Johnson Syndrome
- Suspected severe liver injury

Non-Serious Adverse Events

The following should be reported:

- Non-serious adverse events leading to permanent study drug discontinuation
- All severe non-serious adverse events (regardless of relation to study drug) including severe laboratory abnormalities will be collected except the study outcomes.

Any other non-serious adverse events do not require reporting. However, any adverse event of particular concern to the investigator may be recorded in the eCRF to alert the sponsor.

Reporting Timelines and Processes

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time any signed and dated ICF is obtained until completion of the subject's last study-related procedure (which may include contact for follow-up of safety). Serious adverse events, including those spontaneously reported to the investigator up to the Day 75 (±5d) visit, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document. 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 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.

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 suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/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.

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 serious adverse events that are unlisted (unexpected) and associated with the use of the study drug. The investigator (or sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

12.3.2. Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax, e-mail).

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in 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 drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a clinical study must be reported as a serious adverse event, except hospitalizations for the following:

- Social reasons in the absence of an adverse event
- Surgery or procedure planned before entry into the study (must be documented in the eCRF).

12.3.3. Pregnancy

All initial reports of pregnancy must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, stillbirth, and congenital anomaly) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must discontinue further study treatment.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

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

12.4. Contacting Sponsor Regarding Safety

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

13. PRODUCT QUALITY COMPLAINT HANDLING

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, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

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

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed on the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

The study drug supplied for this study is rivaroxaban 10 mg, rivaroxaban 7.5 mg and matching placebo. All study drugs will be provided as round white tablets. The crushed 10 mg tablet has been studied for bioequivalence and approved for administration as a crushed tablet; the crushed 7.5 mg tablet has not been tested.

Refer to the Investigator's Brochure for a list of excipients [19].

14.2. Packaging

The study drug will be supplied in bottles and dispensed in child-resistant packaging.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation Handling and Storage

The storage recommendation for rivaroxaban is at room temperature (approximately 15° to 30°C).

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented on the drug accountability form. Subjects must be instructed to return all original containers, whether empty or containing study drug.

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study drug will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The

investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator Brochure
- Pharmacy manual/study site investigational product manual
- IWRS Manual
- electronic data capture (eDC) Manual

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. 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 subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

This study was designed to closely mimic current clinical practice of discontinuing anticoagulation at hospital discharge. Over 90% of post-discharge patients do not continue thromboprophylaxis with anticoagulants. Furthermore, thromboprophylactic treatment is limited by the growing trend for shorter hospital stays (see Section 1.1). As VTE events still occur post-hospital discharge, there is a need to evaluate the current standard of care. A placebo comparator group is therefore justified to evaluate this post-discharge treatment paradigm. The bleeding risk will be reduced in this high risk medically ill population through dose adjustment and exclusion of patient subgroups with a comparatively higher bleeding risk, eg, active cancer (see Exclusion Criteria Section 4.2).

Any subject with a medical condition that requires use of any parenteral or oral anticoagulation (eg, atrial fibrillation) during the study is not eligible for participation. During the study, should the subject develop any condition which in the investigator's judgment requires anticoagulation, fibrinolysis, or thromboprophylaxis, the subject will have study treatment discontinued and will be managed as deemed appropriate by the treating physician. The subject will be asked to continue in the study to be followed for efficacy and safety outcomes.

Rivaroxaban has been studied in over 70,000 patients for treating or preventing thrombotic associated diseases. Because the safety profile of rivaroxaban and the risk of bleeding with its use are well known, blood draws were kept to a minimum in this fragile group of subjects. Subjects will undergo all other treatments and diagnostic tests according to the standard of care in their locality, thus making this study minimally intrusive in their regular routine health care.

Investigators should inform the subject of the importance to complete all study visits if their study drug is discontinued prematurely due to an adverse event, or other reasons, in order to assess the vital status and determine if outcome events may have occurred. If these subjects refuse office visits, the investigator should remind the subject about the importance of allowing regular contact until study end, according to the TIME AND EVENTS SCHEDULE, either with them, or with a legally acceptable representative, a close friend or relative, or their primary care physician to determine vital status and if an efficacy or safety outcome event has occurred.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current 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 subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. 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 ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects 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 subjects
- 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 subjects, data or study conduct), the ICF, applicable recruiting materials, and subject 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 subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure 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 drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects 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 subjects, data or study conduct), the amendment and applicable ICF 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. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct).

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the

reviewing IEC/IRB and be in a language that the subject can read and understand. The informed 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.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that if they choose not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access, including permission to obtain information about his or her survival status, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, and subsequent disease-related treatments, or to obtain information about his or her survival status.

If a subject is unwilling or unable to return for a Day 45 (+4d) and/or follow-up Day 75 (±5d) visit, sites should collect as much information as possible, including contacting the subject or legally acceptable representative by telephone or by mail to determine vital status and if an outcome event has occurred, as agreed to by the subject during the initial informed consent process.

The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

If the subject 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 ICF after the oral consent of the subject.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects 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 subjects confidential.

The informed consent obtained from the subject 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 subject 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.

17. ADMINISTRATIVE REQUIREMENTS

17.1. 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 subjects, 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) involves only logistic or administrative aspects of the study, the IRB (and IEC 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 (see Contact Information page(s) provided separately). 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.

17.2. Regulatory Documentation

17.2.1. 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.

17.2.2. Required Pre-study Documentation

The following documents must be provided to the sponsor before shipment of study drug 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, ICF, any recruiting materials, and if applicable, subject 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-site 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 subject:

- 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

17.3. Subject Identification Enrollment and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All

reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the eCRF: subject 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; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly recorded at the study site as a basis for standard medical care. Specific details required as source data for the study 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:

- History of smoking
- Blood pressure and pulse
- Height and weight

17.5. Case Report Form Completion

Case report forms are provided for each subject in printed or electronic format.

Electronic Data Capture (eDC) will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an eCRF, and transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the study site. The electronic file will be considered to be the CRF.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subject's source documentation. All data relating to the study must be recorded in CRFs prepared by the sponsor. Data must be entered into CRFs in English. Study site personnel must complete the CRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

The investigator must verify that all data entries in the CRFs are accurate and correct.

All CRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or an authorized member of the study-site personnel must adjust the CRF (if applicable) and complete the query.

The investigator or study-site personnel must adjust the CRF (if applicable) and complete the query.

If corrections to a CRF are needed after the initial entry into the CRF, this can be done in 3 different ways:

- Study site 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).
- Study site manager can generate a query for resolution by the study-site personnel.
- Clinical data manager can generate a query for resolution by the study-site personnel.

17.6. 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, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review CRFs for accuracy and completeness during on-site monitoring visits and after their return to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. The data will be entered into the study database and verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRFs and all source documents that support the data collected from each subject, 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.

17.8. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. At these visits, the monitor will compare a sample of the data entered into the CRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Remote data surveillance will be performed to monitor the study. Key subject demographic data, site performance data and other key variable data will be monitored remotely as part of routine data surveillance on a monthly basis for all sites and be compared to the results seen overall for that country and region. Sites identified as having subjects with data that deviates substantially from the norm may also be subject to additional in-person monitoring visits.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review of eCRFs and source documents will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

17.9. Study Completion/Termination

17.9.1. Study Completion

The study is considered completed with the last study assessment for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study 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 health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development

17.10. 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 and comparison with the CRFs. Subject privacy must, however, be respected. The investigator and study-site 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.

17.11. Use of Information and Publication

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 exploratory 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 CRF data from all study sites that participated in the study, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's database. 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. Results of exploratory analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject 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 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 outcomes 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 12 months of the availability of the final data (tables, listings, graphs), 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 Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

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Attachment 1: Efficacy Outcomes

All efficacy evaluations and outcomes described in Section 9.2 will be evaluated and adjudicated by the CEC (defined below). Safety outcomes are defined in Section 9.5.

1. Death will be assigned to 1 of the following:
   a. CV death
      i) VTE-related
         (1) VTE-related death – death due to confirmed PE documented by objective testing or autopsy,
         (2) VTE-related, PE cannot be ruled out – death, which cannot be attributed to a documented cause and for which pulmonary embolism cannot be ruled out (unexplained death)
      ii) Other CV death
   b. Non-CV death – death not included in 1 of the above categories

2. Symptomatic DVT – displaying signs or symptoms of proximal or distal lower extremity DVT, upper extremity DVT, or other DVT and confirmed by adjudication, based on 1 or more of the following diagnostic criteria:
   a. a non-compressible venous segment on compression ultrasonography, or in patients 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. DVT documented at autopsy.

   If in patients with history of previous DVT or incomplete documentation of the previous episode is available, additional criteria may be integrated into the adjudication of 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

3. Symptomatic PE – displaying signs or symptoms suggestive of PE and confirmed by adjudication based on 1 or more of the following diagnostic criteria:
   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 patient, evidence of right ventricular dysfunction by transthoracic or trans esophageal echocardiogram (ESC criteria), or
   f. PE documented at autopsy.

   The anatomic extent of PE will be classified by the adjudication committee as either segmental or greater, or sub-segmental. The totality of available clinical, imaging and laboratory findings should be considered.

4. Myocardial infarction
   Requires combination of evidence of myocardial necrosis (either changes in cardiac biomarkers or post-mortem pathological findings), and supporting information from clinical presentation, ECG changes or the results of myocardial imaging or coronary artery imaging. The totality of available clinical, ECG and cardiac biomarker should be considered:
   1. Clinical Presentation consistent with the diagnosis of myocardial ischemia and infarction, taking into account differential conditions associated with elevations in cardiac biomarkers
   2. Biomarker elevations
      a. Elevations relative to URL in CK, CK-MB or troponin
   3. ECG changes
      a. ECG manifestations of acute myocardial ischemia (in absence of left ventricular hypertrophy and left bundle branch block); abnormalities may be lesser in patients with abnormal biomarkers
         i. New ST elevation at the J point in 2 contiguous leads with the cut-points: ≥0.1 mV in all leads other than leads V2-V3 where the following cut-points apply: ≥0.2 mV in men ≥40 years (≥0.25 mV in men <40 years) or ≥0.15 mV in women
         ii. New horizontal or down-sloping ST depression ≥0.05 mV in 2 contiguous leads and/or new T inversion ≥0.1 mV in 2 contiguous leads with prominent R wave or R/S ratio>1
      b. Criteria for pathological Q-wave
         i. Any Q-wave in leads V2-V3 (abnormalities may be lesser in patients with abnormal biomarkers) 0.02 seconds or QS complex in leads V2 and V3
         ii. Q-wave ≥0.03 seconds and ≥0.1mV deep or QS complex n leads I, II, aVL, aVF, or V4-V6 in any 2 leads of a contiguous lead grouping (I, aVL, V1-V6, II, III, and aVF; the same criteria are used for supplemental leads V7-V9 and for the Cabrera frontal plane lead grouping)
      c. ECG changes with prior myocardial infarction
         i. Pathological Q-waves, as defined above
         ii. R-wave ≥0.04 seconds in V1-V2 and R/S≥1 with a concordant positive T-wave in the absence of a conduction defect
      d. Criteria for prior myocardial infarction
         i. Pathological Q waves with or without symptoms in the absence of non-ischemic causes
         ii. Imaging evidence of a region of loss viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic change
         iii. Pathological findings of a prior myocardial infarction

5. Stroke – an acute episode of focal or global neurological dysfunction caused by non-traumatic brain or spinal cord injury as a result of hemorrhage or infarction

Attachment 2: Suspected Event Supporting Documentation

The following supporting material, if available, will be requested to be submitted for each suspected event by the investigative site. The totality of available clinical, imaging and laboratory findings should be considered. Supporting materials to be completed/collected, not limited to:

1. Death with cause
    1. Complete Death eCRF data
    2. Hospital admission history and physical/death summary
    3. Autopsy reports

2. Suspected Symptomatic deep venous thrombosis (DVT)

    1. Complete Symptomatic Deep Vein Thrombosis eCRF data
    2. Imaging
    3. Hospital admission history and physical
    4. Hospital discharge summary
    5. Duplex ultrasound
    6. Venography
    7. Computed tomography (CT) scan or MRI
    8. D-Dimer
    9. Autopsy reports

3. Suspected Symptomatic PE

    1. Complete Symptomatic Pulmonary Embolism eCRF data
    2. Hospital admission history and physical
    3. Hospital discharge summary
    4. D-Dimer
    5. High resolution CT pulmonary angiogram or helical chest CT scan
    6. Ventilation/perfusion scan
    7. Transthoracic or transesophageal echocardiogram in hemodynamically unstable patient
    8. MRI
    9. Chest X-Ray
    10. Duplex Ultrasound or venography
    11. Electrocardiogram
    12. Autopsy reports

4. Suspected Myocardial infarction / acute coronary syndrome

    1. Complete Myocardial Infarction eCRF data
    2. Hospital admission history and physical
    3. Hospital discharge summary
    4. Electrocardiogram
    5. Cardiac Biomarkers
    6. Autopsy reports

5. Suspected Stroke / transient ischemic attack

    1. Complete Stroke eCRF data
    2. Hospital admission history and physical

3. Hospital discharge summary
4. Computed tomography (CT) scan
5. Magnetic resonance imaging (MRI)

6. Suspected Major bleeding (MB)

    1. Complete Bleeding Event eCRF data
    2. Hospital admission history and physical
    3. Hospital discharge summary
    4. Procedure notes
    5. CBC laboratory test

7. Suspected Non-major clinically relevant bleeding (NMCR)

    1. Complete Bleeding Event eCRF data
    2. Hospital admission history and physical
    3. Hospital discharge summary
    4. Procedure notes
    5. CBC laboratory test

8. Suspected Other Bleeding

    1. Complete Bleeding Event eCRF data
    2. Hospital admission history and physical
    3. Hospital discharge summary
    4. Procedure notes
    5. CBC laboratory test

Attachment 3: Pharmacokinetic Sample Collection and Handling

Materials and Labeling

Blood must be collected in glass or plastic blood collection tubes (eg, Vacutainer®) containing appropriate anticoagulants. Resulting plasma samples must be stored in polypropylene storage tubes. No tubes with separation gel should be used.

Use of alternative materials will not result in a protocol amendment if preapproved by the Bio-analysis Scientist.
All tubes and containers will be labeled with preprinted labels. The preprinted information will include the study number, CRF identification number (CRF I.D. #), treatment arm or treatment period, scheduled sampling day and time as stipulated in the flow chart, and the analyte name if applicable. No other information will be written on the labels. Labels should be attached to the storage tubes at least 12 hours before being frozen to ensure proper adherence.

Labels should be applied to the sample tubes as follows:

- Apply labels to the sample tubes so that they do not overlap and obscure any information. If possible, expose an area between the 2 ends of the label to allow viewing of the contents of the tube.
- Do not alter the orientation of the label on the sample tube.
- Apply labels to all tubes in the same manner.

Preparation of Plasma Pharmacokinetic Samples for Rivaroxaban

- Collect 2 mL of blood into the appropriate K_2EDTA -containing collection tube (eg, Vacutainer) at each time point.
- Record the exact date and time of sampling in the CRF.
- Gently invert the tubes 8 to 10 times to afford mixing, before processing.
- Centrifuge blood samples at room temperature within 1 hour of collection in a clinical centrifuge at 1,300 g for 15 minutes or centrifuge for 10 minutes at 1,500 - 1,600 g, unless otherwise specified by the supplier, to yield approximately 1 mL of plasma from each 2 mL whole blood sample.
- Transfer all separated plasma immediately with a clean, disposable glass or polyethylene pipette (use 1 new pipette per sample) to a pre-labeled storage tube (1.8 mL NUNC tubes).
- Store plasma samples in an upright position in a freezer, at a set temperature of -20°C until transfer to the bio-analytical facility.
- The time between blood collection and freezing the plasma will not exceed 2 hours.
- Ship specimens according to the instructions provided.
- Ship specimens to the bio-analytical facility, sorted by subject, by sample collection date and time.
- Questions regarding handling the plasma PK specimens should be addressed to the contact person for the sponsor.
- Alternative procedures will not result in a protocol amendment if approved by the Bioanalysis Scientist.

Please refer to the Study Lab Manual for proper shipping instructions.

Attachment 4: Symptom Assessment

During all contacts, the treatment and clinical course of the subject is to be evaluated using a standard list of questions. Please ask the subject systematically the following questions -

1. **Since the last contact did you experience new or increased?**

Shortness of Breath	Yes ☐ No ☐
Chest Pain especially while breathing	Yes ☐ No ☐
Cough	Yes ☐ No ☐
Blood in Sputum	Yes ☐ No ☐
Dizziness or Fainting	Yes ☐ No ☐
Rapid Breathing	Yes ☐ No ☐
Rapid Heart Rate	Yes ☐ No ☐
Blue Lips or Fingers	Yes ☐ No ☐
Weakness on one side of face/body	Yes ☐ No ☐
Fever	Yes ☐ No ☐

If PE is clinically suspected, perform objective testing and complete the adjudication package as described in Attachment 2 **(Suspected Event Supporting Documentation)** of the protocol.

2. **Since the last contact did you experience new or increased?**

Calf pain, tenderness or swelling	Yes ☐ No ☐
Appearance of veins on the surface of the skin on legs	Yes ☐ No ☐
Tenderness along deep veins of legs	Yes ☐ No ☐
Swelling of entire leg	Yes ☐ No ☐
Puffiness of leg	Yes ☐ No ☐

If DVT is clinically suspected, perform objective testing and complete the adjudication package as described in Attachment 2 **(Suspected Event Supporting Documentation)** of the protocol.

3. **Since the last contact did you experience any?**

Bleeding	Yes ☐ No ☐

If yes, complete the adjudication package as described in Attachment 2 **(Suspected Event Supporting Documentation)** of the protocol.

Attachment 5: INT-1 to INT-5 / Amendment Changes

Amendment INT-5 (15 June 2015)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reasons for the amendment are to modify study procedures (including the risk score criterion) and to add patient training material.

Applicable Section(s)	Description of Change(s)

Rationale: Emerging literature has indicated that the required risk score of the subjects enrolled were not sufficient to attain the desired event rate. Because the outcome events are all symptomatic in this study, additional site and subject training is necessary to ensure capturing events.

Applicable Section(s)	Description of Change(s)
Synopsis Objective and Hypothesis: Secondary Objectives, Exploratory Objectives, Hypothesis, Section 2.1, Objectives, Section 2.2, Hypothesis, 11.3.Efficacy Analyses, Secondary Efficacy Outcomes	Definition of VTE-related death was added. . Composite outcome was added to Secondary Objectives and Hypothesis.
Synopsis Overview Of Study Design, Section 3.1, Overview of Study Design	Definition of VTE-related death was added. CHF was replaced with HF with reduced LVEF. Upper limit of index hospitalization was changed to 10 days. Additional inclusion criterion regarding VTE risk score was added. Figure 3 was replaced and the new figure updates index hospitalization.
Synopsis Subject Population	CHF was replaced with HF with reduced LVEF. Upper limit of index hospitalization was changed to 10 days. Additional inclusion criteria regarding VTE risk score were added.
Synopsis Dosage and Administration, Interruption of Study Drug	Statement that study drug needs to be discontinued was replaced with 'temporarily interrupted'. Clarifications regarding use of anticoagulation thromboprophylaxis were added.
Synopsis Efficacy Evaluations/Outcomes	Definition of VTE-related death was added. The composite outcome was added to efficacy outcomes.
Synopsis Exploratory Objectives	"Symptomatic" was added to upper extremity DVT and the composite outcome was deleted.
Synopsis Dosage and Administration	Clarification was added that "Regardless of the day on which the Day 45 Visit occurs, no study drug may be taken after Day 45".

Applicable Section(s)	Description of Change(s)
Time and Events Schedule, and Section 9.1.2. Screening Phase	Treatment window upper limit on Day 7 and Day 21 was modified. Protocol activities were further clarified by modifying or adding more detailed footnotes, ie, admitting diagnosis, D-dimer screening, training on signs and symptoms of disease. Symptom Assessment and Subject Counseling were added. Consent language was changed to allow for screening to occur any time after admission of index hospitalization and once the informed consent is obtained. Also, drug accountability/dispensation at Day 7 was removed and Day 7 visit may now be performed by telephone.
Synopsis Statistical Methods, Sample Size Determination, Efficacy Analyses	Further details were added regarding stop of randomization. Definition of VTE-related death was added. The composite outcome was added to efficacy analyses.
Throughout the protocol	Definition of VTE-related death was added. CHF was replaced with 'HF with reduced LVEF'.
Section 1.1.5, Studies Examining Extended Thromboprophylaxis in Patients Hospitalized for Acute Medical Conditions and MARINER Approach	Addition of paragraph regarding IMPROVE VTE risk score and missed diagnosis of PE.
Section 3.2, Study Design Rationale	Clarification regarding comparator treatment discontinuation was added. Non-hemorrhagic was deleted from non-hemorrhagic stroke.
3.3.1, Executive Committee	Addition of ad hoc member appointment as necessary.
Section 3.3.3, Clinical Events Committee	Suspected outcome events were modified for DVT, MI, stroke, and bleeding.

Applicable Section(s)	Description of Change(s)
Rationale: Modified inclusion criteria to enrich for subjects with higher level of risk of VTE and to align with standard of care for stroke patients.	
4. SUBJECT POPULATION, Section 4.1 Inclusion Criteria.	Consent language was changed to allow for screening to occur any time after admission of index hospitalization and once the informed consent is obtained. For Sections 4.1. Inclusion Criteria, 4.2. Exclusion Criteria and 4.3. Prohibitions and Restrictions, detailed protocol amendment modifications are described in Attachment 6, and a shorter version is provided in-text. Inclusion Criterion # 1. The allowed duration of the hospitalization was decreased from 14 to 10 days. Detail was added regarding the type and extent of CHF present to be eligible for the study. Patients with preserved ventricular function will not be enrolled because of the lower risk of VTE than in patients with reduced ventricular function. In the previous version of the protocol (INT-4), subjects were not allowed to have received fibrinolysis during the index hospitalization. This has been updated based on the standard of care for stroke patients. Inclusion Criterion # 2. An elevated D-dimer will now be required to be eligible if the VTE risk score is 2 or 3. Direction to verify at randomization that the IMPROVE Risk Score calculated at screening was calculated correctly. In Table 1, the footnote was simplified to mirror the cancer exclusion. Inclusion Criterion # 4. Maximum daily dose of thromboprophylactic agents allowed was added to ensure that subjects have not received off-label use of thromboprophylaxis.
Rationale: Modified exclusion criteria to align with standard of care and to provide more clarity for enrollment.	
Section 4.2 Exclusion Criteria.	Exclusion Criterion #1. The phrase about recent bleeding that would allow the investigator to make a determination of whether or not the bleeding would contraindicate the use of pharmacologic thromboprophylaxis was removed. Exclusion Criterion #2. Guidance on differentiating major from minor surgery has been added. According to the standard of care, ongoing thromboprophylaxis is generally not discontinued for the performance of cataract surgery, so the notation that recent cataract surgery is not an exclusion criterion has been added. The exclusion period for recent head trauma was reduced from 3 months to 4 weeks, based on expert input. Exclusion Criterion #3. Reference was changed for consistency with the new location of the item referenced. Exclusion Criterion #5. Addition of any intracranial bleeding. Exclusion Criterion #6 was removed. Exclusion Criterion #7. For intracranial neoplasm, it was clarified that the presence of either a malignant or a benign neoplasm would result in exclusion. Exclusion Criterion #10. Subjects with cancer not in remission will be excluded. The previous requirement for a remission of at least 6 months duration has been removed, allowing the clinician to determine what time period is appropriate.

Applicable Section(s)	Description of Change(s)
	Exclusion Criterion #19. Use of an intravascular device for blood pressure support during the index hospitalization was added as an exclusion because the vascular access required for the use of such devices would present an unacceptable bleeding risk. Exclusion Criterion #23. In the previous version (INT-4) of the protocol, it was specified that the use of fibrinolysis during the index hospitalization precluded inclusion in the study. This has been modified to accommodate the inclusion criterion revision that allows the inclusion of subjects with ischemic stroke and use of fibrinolysis, if fibrinolysis occurred at least 3 days before randomization. Exclusion Criterion #24. The antiplatelet exclusion criteria have been grouped together and the prohibition of use of these antiplatelet regimens has been extended to the beginning of the index hospitalization instead of planned use during the study. Exclusion Criterion #27 was removed and was added to the list of medications excluded at index hospitalization within Exclusion Criterion #24. Exclusion Criterion #28. Use of NSAIDs was further clarified. Exclusion Criterion #31. The exclusion criterion related to PPIs and clopidogrel concomitant use has been removed as the drugs discussed are not study treatments.
Rationale: Modified exclusion criteria to align with standard of care and to provide more clarity for enrollment.	
Section 4.3. Prohibitions and Restrictions	Discontinuation of the study drug was further clarified. Criteria #1 and #5 were removed and content was added to criterion #7.1. Criterion #7. The antiplatelet exclusion criteria have been grouped together and the prohibition of use of these antiplatelet regimens has been extended to the beginning of the index hospitalization instead of planned use during the study.
Section 5. Treatment Allocation and Blinding, Treatment Allocation, Unblinding	To allow the ability to achieve a regionally heterogeneous population, this change allows the sponsor to cap enrollment by region without a protocol amendment. A header identifying the position of description of unblinding processes has been added to better direct the reader. A statement was added to indicate that even in the event of an outcome or bleeding event, an investigator will be able to unblind a subject's treatment.
Section 5 Treatment Allocation and Blinding, Section 6. Dosage and Administration, Interruption of Study Drug, 10.2.1. Temporary Interruption of Study Treatment, Section 10.2.2 Approach to Subjects with Dose Interruption, Section 7. Treatment Compliance, Section 9.2.2. Approach to the Subject with an Efficacy Outcome Event	Study drug interruption and drug accountability were further clarified, and minor modifications were made to Table 6.

Applicable Section(s)	Description of Change(s)
Section 8. Prestudy and Concomitant Therapy	Further clarifications were added on medications taken during the index hospitalization and recording of drug identities.
Section 9.1.2. Screening Phase, 9.5.3.Other Safety Assessments	A baseline D-dimer screening was added to assess its contribution to VTE risk in the study population.
Section 9.1.3. Double-Blind Treatment Phase	Details for the randomization and treatment visits were added to guide the reader.
Section 9.1.4. Post-treatment Phase (Follow-Up)	Details for follow-up visit were added.
Section 9.2. Efficacy Evaluations and Outcomes	Paragraph was added regarding the judicious diagnosis of PE by the investigators.
Section 2.1. Objectives, Section 9.2.1. Efficacy Evaluations and Outcomes	Requirements for submission of a suspected event for adjudication were added. For exploratory efficacy outcomes, “Symptomatic” was added for clarification to “Upper extremity DVT”.
Section 9.5.1. Bleeding Events, 11.6. Safety Analyses, Bleeding Outcomes	Additional resource for CEC classification of bleeding events was added.
Section 11.2. Sample Size Determination	Further details were added regarding stop of randomization.
Section 11.3. Efficacy Analyses	For subgroup analyses, geographic regions were added, and admitting diagnosis was modified.
Section 11.8. Benefit-Risk Analysis	A bivariate approach to benefit-risk assessment that will be explored was added.
Section 12.3.1. All Adverse Events	Non-hemorrhagic was deleted from non-hemorrhagic stroke. Adverse event reporting was clarified further.
Section 14.1. Physical Description of Study Drug(s)	Information about crushed tablets was added.
References	List was updated.
Attachment 1: Efficacy Outcomes	Assignment of death was modified for clarity. Stroke was modified for clarity (eg, non-hemorrhagic was removed).
Attachment 2: Suspected Event Supporting Documentation	All events, with the exception of death, were defined as suspected. For 4.) Suspected MI/ACS, Cardiac Biomarkers are now included for supporting documentation.
Attachment 4: Symptom Assessment	Attachment was added to capture clinical status for suspected outcome events and symptom assessment.
Attachment 5: INT-1 to INT-4/ Amendment Changes, and	Attachment was added to the protocol.
Attachment 6: Complete Amendment History of INT-5 Inclusion and Exclusion Criteria, and Prohibitions and Restrictions for Data Collection Purposes	Attachment was added to the protocol.
Throughout the protocol	Minor grammatical, formatting, and spelling changes were made.

Amendment INT-4 (19 January 2015)	
This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.	
The overall reason for the amendment: The overall reason for the amendment is to provide further clarifications.	
Applicable Section(s)	Description of Change(s)
Rationale: Clarification of study design and the correction to exclusionary medications.	
Applicable Section(s)	Description of Change(s)
Time and Events Schedule, and Section 9.1.2. Screening Phase	Minor edits to footnotes for clarification.
Section 4.2 Exclusion Criteria.	Exclusion criteria # 2.1 and #3.1 modified with correct references in parenthesis. Exclusion criteria #22.2.a and #22.2.b modified to specify correct exclusionary medications.
Section 4.3 Prohibitions and Restrictions	Prohibitions and Restrictions criteria #2 and 3 modified to specify correct exclusionary medications.
Amendment INT-3 (8 December 2014)	
This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.	
The overall reason for the amendment: The overall reason for the amendment is to provide further clarifications in response to questions from regulatory agencies and investigator sites	
Applicable Section(s)	Description of Change(s)
Rationale: Clarification of study design, simplification of conduct, to enhance data collection, also to avoid scheduling difficulties, or subject population (in response to comments from sites in attendance at investigator meetings, health authority, site, or Ethics Committee queries), and congruent to the Statistical Analysis Plan.	
Synopsis Objective and Hypothesis: Primary Objective, Secondary Objectives, Exploratory Objectives, Hypothesis, Efficacy Evaluations/Outcomes; Section 2.1. Exploratory Objectives; Section 2.2. Hypotheses; Section 9.2. Efficacy Evaluations and Outcomes	Increased the level of detail in the exploratory objectives. For symptomatic DVT, the additional descriptor "lower extremity" was added. For symptomatic PE, "non-fatal" was added in keeping with the SAP. For CV events, "fatal and non-fatal" was removed as the combination results simply in all CV events. The paragraph “If a subject….drug treatment” was added to clarify that unblinding is unlikely to impact the care of the subjects. The paragraph “Rivaroxaban will not be….benefit from study treatment” has been added as an explanation of whether or not study treatment will be provided after the subject completes participation in the study.

Applicable Section(s)	Description of Change(s)
Synopsis Overview of Study Design; Section 3. Study Design and Rationale Synopsis Subject Population; Section 3.1. Overview of Study Design; 4.1 Inclusion Criteria	Re-worded subject population for better interpretation. The term "hospital discharge" has been removed and replaced with “leaving the hospital”, The phrase “new onset or exacerbation” has been added to reinforce that the reason for the hospitalization that qualifies a patient for inclusion is broadly defined. The phrase “including spinal cord infarction” has been moved from its own inclusion criterion to be closer to the reason for hospitalization that it modifies. The phrase, “placebo…hospital discharge” has been added to provide a rationale for selection of placebo as the comparator, with a more extensive explanation later in the protocol.
Time and Events Schedule	Minor edits, including addition of Discharge Destination to all visits, and change from +3d to +4d for the Day 45 visit. Reformatted, added, and renamed protocol activity, eg, added LMWH/UFH use and index hospitalization and modified footnotes eg, collection of hemoglobin, , platelet count, vital signs clinical assessment requirement and criteria, and CrCl, D-dimer, fasting and PK samples, and instructions regarding discontinuing for consistency with protocol body and eCRF. Deleted hematocrit, hemogram (CBC) and auto differentiation.
Section 4.1 Inclusion Criteria.	Inclusion Criteria 1, 2, 3, 4, and 6 were modified and Inclusion Criterion 5 was deleted. Specifically: Inclusion Criterion #1 was divided into 3 sub-criteria, “index hospitalization” definition added to improve the clarity of counting the number of days, term “hospital discharge” has been removed and “the day the patient leaves the hospital” has been edited. Inclusion Criterion #2, the explanations in the footnotes of the risk score table were expanded with content of INT-2 Appendices, age modified from > to ≥60 and split into 2 sub-sections to enhance data collection, and guidelines for the definition of major surgery have been added. Inclusion Criterion #3, term “post-discharge” has been removed as unnecessary. Inclusion Criterion #4, concrete guidance added regarding thromboprophylaxis. Inclusion Criterion #5 deleted and content now incorporated into inclusion criterion #1. Inclusion Criterion #6 modified to exclude legally acceptable representatives from providing informed consent.

Applicable Section(s)	Description of Change(s)
Section 4.2, Exclusion Criteria	Criteria 2, 3, 5, 5, 6, 9, 10, 11, 12, 14, 15, 1822, 23, 24, 25, 26, 27, and 28 were modified. Criterion 31 was added. Specifically: Exclusion Criterion #2 and #3, added references to the guidelines for the definition of major surgery. Exclusion Criterion #4 modified to allow for normalization of the INR during the index hospitalization. Exclusion Criterion #5 modified to include information that was formerly provided in an appendix. Exclusion Criterion #6 modified to provide guidance clarifying the meaning of "severe head trauma". Exclusion Criterion #9 modified to allow for normalization of or spurious platelet counts during the index hospitalization. Exclusion Criterion #10 modified to clarify that non-melanoma skin cancer is not an exclusion criterion and that leuprolide acetate is not a prohibited medication. Exclusion Criterion #11modified to specify the anticoagulants that are prohibited. Exclusion Criterion #12, added unilateral below the knee amputation. Exclusion Criterion #14 modified to include a reference to calculating the creatinine clearance. Exclusion Criterion #15 modified to indicate that the degree of liver insufficiency which would result in exclusion is liver disease associated with a coagulopathy. Exclusion Criterion #18 modified to allow the investigator to use discretion in determining the degree of alcohol abuse that would lead to exclusion from the study. Exclusion Criterion #22 modified to include both inducers and inhibitors and the most up-to-date language. Exclusion Criterion #23 modified to remove "systemic" as any fibrinolysis during the index hospitalization will result in exclusion, and that actual receipt of a fibrinolytic would result in exclusion. Exclusion Criterion #24 divided into 2 sub-sections to allow for enhanced data collection and a note has been added to indicate that dipyridamole is allowed. Exclusion Criterion #25 modified to reflect current standard language. Exclusion Criterion #26, minor wording changes. Exclusion Criterion #27, minor wording changes. Exclusion Criterion #28 minor wording changes. Exclusion Criterion #31added to reflect the usual exclusion criteria language for the drug under study.
Overview of Study Design, Section 3.1 Overview of Study, Section 4.1, Inclusion Criteria	Definition of index hospitalization has been added to clarify the way days are counted for the index hospitalization.
Overview of Study Design, Section 3.1 Overview of Study Design, 9.1.3. Double-Blind Treatment Phase	The definition of "discharge" has been clarified further, to allow the sites more flexibility with the timing of randomization relative to hospital discharge.

Applicable Section(s)	Description of Change(s)
Section 1.1 Background, Sections 1.2 Overall Rationale for the Study, Section 3.1 Overview of Study Design, Dosage and Administration, Efficacy Analyses, Section 3.2 Blinding Control Study Phase/Periods Treatment Groups, 3.2 Dose Selection, 3.2 Pharmacokinetics Analysis, Section 5 Treatment Allocation & Blinding, Section 6. Dosage and Administration, Attachment 1, Section 11.3 Primary Efficacy Outcome	To provide clarity regarding stratum assignment for subjects with CrCl >30 and <49 mL/min was changed to CrCl ≥30 and <50 mL/min.
Synopsis Choice of Safety Measures, Section 3.2 Study Design Rationale, Section 12.3.1 All Adverse Events	Addition of acute coronary syndrome and transient ischemic attack as serious adverse events.
Section 3.2 Study Design Rationale	Provided rationale for placebo comparator selection.
Overview of Study Design, Section 3.1 Overview of Study Design, 6. Dosage and Administration	Reinforced that the first dose of study drug should be administered as soon after randomization as possible. Diagram of study design updated to reflect changes.
Overview of Study Design, Section 3.1 Overview of Study Design, 4.1 Inclusion Criteria Section 1.1 Background	Parenteral anticoagulation requirement (LMWH, UFH) and duration were specified.
Section 3.3.3 Clinical Events Committee	Events to be adjudicated were clarified.
Section 4. Subject Population	Clarified time to screening subjects relative to “discharge from hospital” and to “index hospitalization”.
Section 4.1 Inclusion Criteria, 16.2.3 Informed Consent, Section 16.2.4 Privacy of Personal Data	Deleted option for legally acceptable representative to sign the informed consent on behalf of the subject.
Section 4.3 Prohibitions and Restrictions	Revised section to match exclusion criteria and detailed concomitant therapy that should not be administered before or during study and clarified restrictions.
Section 5 Treatment Allocation and Blinding	Added statement for risk factor groups to allow for a heterogeneous population. Paragraph was added to clarify that unblinding is unlikely to impact the care of the subject.

Applicable Section(s)	Description of Change(s)
Synopsis Dosage and Administration, Section 6. Dosage and Administration	Added clarification regarding the chronic therapy with rivaroxaban. Added comment about dosing in the event of a change in creatinine clearance. Added instructions about timing of first dose of study drug administration. Added paragraph about whether study drug will be provided after the subject completes study participation.
Section 9.1.2. Screening Phase	Clarification was added regarding when screening activities may begin. Statement was added regarding local D-dimer laboratory collection. Added the details on creatinine clearance calculations, and deleted from INT-2 attachment.
Section 9.1.3. Double-Blind Treatment Phase	Added more reasons for unscheduled visits and timing and location of randomization have been simplified and broadened.
Section 9.1.3 Post-treatment Phase (Follow-Up)	Added paragraph about whether study treatment will be provided after the subject completes study participation.
Section 9.2.1. Efficacy Evaluations and Outcomes	Added further clarification to outcome event processing, and adding ACS and TIA to encourage the investigator that events that suggest the possibility of MI or stroke be sent for adjudication. Added instructions about the handling of images for enhanced submitting CEC packages.
Section 9.2.2 Approach to the Subject with an Efficacy Outcome Event	New section added to provide guidance to treating physician for efficacy outcomes events.
Section 9.3.1 Evaluations	Modified to include non-fasting status for PK sampling.
Section 9.5 Safety Evaluations and Outcomes: Clinical Laboratory Tests	Serum pregnancy test added as an option to match the Time And Events Schedule.
Section 9.5.2. Approach to the Subject with a Bleeding Event	New section added to provide guidance for serious bleeding events.
Synopsis, Dosage and Administration, Section 3.2 Study Design, Section 10.2 Discontinuation of Study Treatment, 10.2.1 Temporary Discontinuation of Study Treatment, 16.1 Ethical Aspects.	Added further guidance on any condition that in the investigator's judgment requires anticoagulation, thromboprophylaxis, or fibrinolysis. Added instructions about possibility for restarting study drug in the event that a low platelet count is noted
Section 10.2.1. Temporary Discontinuation of Study Treatment	Added instructions about possibility for restarting study drug in the event that a low platelet count is noted.
Section 10.2. Discontinuation of Study Treatment	Added paragraph about management in the event that the subject develops a need for anticoagulation.
Section 10.2.2. Approach to Subjects with Dose Interruption	Moved section from previous INT-2 Attachment for increased accessibility of the information.

Applicable Section(s)	Description of Change(s)
Section 10.2.3 Permanent Discontinuation of Study Treatment	Added an additional criterion for discontinuation of study treatment to allow for drops in creatinine clearance to below the level that resulted in exclusion from the study.
Section 12.3.1 All Adverse Events	Section was modified and for more clarity, with addition of ACS and Transient ischemic attack, and new sub-categories, ie, Serious Adverse Events, Non-Serious Adverse Events, and Reporting Timelines and Processes. ACS and TIA events will be sent for adjudication.
Section 12.3.3 Pregnancy	Added clarifications regarding partner pregnancy and infant follow-up.
Section 16.1. Study-Specific Design Considerations	Added guidance regarding required use of parenteral or oral anticoagulation.
Section 17.4 Source Documentation	Race was removed as an item recorded directly into the eCRF.
Throughout the protocol	Minor editorial changes. Added "lower extremity" to symptomatic DVT, added "non-fatal" to symptomatic PE.
Attachments, Attachment 1, Efficacy Outcomes	Added Attachment 2, Event Supporting Documentation. Moved INT-2 Attachments 1, 2, 3, and 4 to main body of protocol. For INT-3 Attachment 1, the definitions of prior INT-2 Attachment 5 were updated to match the CEC charter.
Rationale: Modified safety and exclusion measures to ensure that adverse events secondary to the study agent are captured correctly.	
Section 3.2 Choice of Safety Measures	Included ACS and transient ischemic attack as measures of efficacy.
Section 12.3.1. All Adverse Event	Section updated to provide clarification and addition of ACS and TIA as events to be exempt from unblinding and expedited reporting.
Rationale: Clarifications added to ensure consistency (eg, with charter, USPI)	
Section 3.3.3 Clinical Events Committee.	Added 'other bleeding' to list of events to be adjudicated by CEC.
Section 4.2 Exclusion Criteria	Revised criterion related to strong CYP3A4 inhibitors and inducers.
Amendment INT-2 (11 April 2014)	
This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.	
The overall reason for the amendment: The overall reason for the amendment is to provide clear description on study procedures.	
Applicable Section(s)	Description of Change(s)
Rationale:	Clarification on baseline values.
Time and Events Schedule and 9.1.2. Screening Phase	Clarifications that the latest value will be taken as baseline if there are multiple values during screening period and that complete blood count and CrCl must be performed/calculated within defined time window before hospital discharge.

Applicable Section(s)	Description of Change(s)
Section 3.3. Committees	Deleted section based on decision not to form a Steering Committee.
Synopsis Section 11. Statistical Methods	Replaced analysis population with analysis set to comply with International Conference on Harmonisation [ICH] E9 guideline.
Section 11.3. Efficacy analyses	Changed the subgroup definition to include the agent used (LMWH or UFH).
Section 12.3.1. All Adverse Events	Deleted "e-CRF" to address an inconsistent description in the section.

Amendment INT-1 (14 March 2014)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.

The overall reason for the amendment: The overall reason for the amendment is to provide clear descriptions and/or definitions on study endpoints, visits, procedures, and terms.

Applicable Section(s)	Description of Change(s)
Rationale: To provide more clarity on the EOT and EOS clinic visits and total study duration.	
Synopsis; 3.1. Overview of Study Design	Deletion of both the 30-day time point follow-up contact, and phone call as follow-up option.
Time and Events Schedule	Addition of "EOT" to Header column for Day 45 and "EOS" for Day 75.
7. Treatment Compliance	Additional clarification regarding treatment compliance on Day 45.
10.1. Completion	Replacement of statements regarding completion of the study with clarifying information on expected total duration of 75 days after randomization.
16.2.3. Informed Consent	Deletion of redundant collection information for subjects unable to return for an EOT and follow-up (EOS) visit.
Rationale: To emphasize zero tolerance on missing endpoint data.	
Throughout the protocol	Where appropriate, addition of "and other outcomes" to "vital status.
Rationale: To provide more clarity, including the definition of terms.	
Throughout the protocol	"Observation period" was changed to "analysis phase". "Approximately" was added to 9,000 subjects. The IDMC charter was deleted.
11.6. Safety Analyses	"Temperature" was deleted from the vital signs that will have descriptive statistics provided.
Rationale: To provide more clarity on potential IDMC recommendations.	
Throughout the protocol	Clarification that the IDMC can recommend to modify and terminate the study prematurely for safety.
Rationale: To delete redundant and unclear expressions as any single missing dose will be captured in eCRF.	
6. Dosage and Administration	Deletion of statement that an occasionally forgotten dose need not be recorded, and limitation of reporting to unintentional stopping of study drug for >7 days.

Applicable Section(s)	Description of Change(s)
Rationale: To reflect that hematocrit values are not part of the ISTH definition for major bleeding.	
9.5. Safety Evaluations and Outcomes	Deletion of stated reduced drop in hemoglobin based on hematocrit values.
Rationale: Clarification that VTE is also a condition that requires permanent anticoagulation.	
10.2.2. Permanent Discontinuation of Study Treatment	Addition of "VTE" as an example for a condition which requires permanent anticoagulation that will result in permanently discontinuing a subject from study drug.
Rationale: For consistency with T&E.	
17.4. Source Documentation	Deletion of heart rate as source data for the eCRF.
Rationale: Update of instructions in Attachment 6 for sample analysis at the bioanalytical lab chosen for the study.	
Attachment 6: Pharmacokinetic Sample Collection and Handling	Addition of K_2EDTA usage for the preparation of plasma PK samples for rivaroxaban. Correction of blood sample centrifugation time to 1 hour. Addition of statement regarding the Study Lab Manual for proper shipping instructions.
Rationale: To avoid miscommunication of the applicable procedures for labeling and shipment of PK samples.	
Attachments 7 and 8	Deletion of both attachments.

Attachment 6: Complete Amendment History of INT-6 Inclusion and Exclusion Criteria, and Prohibitions and Restrictions for Data Collection Purposes

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study.

1. Criterion Modified per Amendment INT-3

1.1. Criterion Modified per Amendment INT-5

1.2.

a. Subject must be a man or woman, ≥40 years of age.

b. The duration of the index hospitalization must have been at least 3 and no more than 10 consecutive days.

The index hospitalization is defined as a hospitalization that ended on the day of or the day before randomization and is a continuous period of time at an acute care facility (including hospital, observation unit, ER and/or transferring facility; collectively referred to as "hospital"). The first day that the subject spends any part of the day in the hospital will be counted when determining the duration of the index hospitalization, but the day the patient leaves the hospital will not be counted.

c. The reason for the index hospitalization must have been a new diagnosis or exacerbation of 1 of the following medical conditions:

- Heart Failure (HF)

  Subject must have a documented LVEF ≤45% within 1 year before randomization or during the index hospitalization. The ejection fraction may be determined by one of the following methods: echocardiogram, nuclear multi-gated acquisition (MUGA) scan, cardiac magnetic resonance imaging (MRI), cardiac computed tomography (CT) scan, or left ventriculography). If more than 1 value for LVEF is available, the most recent one should be used.

- Acute respiratory insufficiency or acute exacerbation of COPD

- Acute ischemic stroke (including spinal cord infarction if no evidence of intramedullary, subdural or epidural hemorrhage)

  If the subject received fibrinolysis as part of the initial treatment for stroke, fibrinolysis must have been administered at least 3 full days before the subject is randomized. These subjects must have had a CT/MRI scan at presentation and a repeat scan performed at least 24 hours after administration of fibrinolysis that documents the absence of hemorrhage. Subjects with hemorrhagic transformation of an ischemic infarct prior to randomization are not excluded unless there is evidence of parenchymal hemorrhage (types PH-1 and PH-2). All planned diagnostic tests for stroke evaluation must be completed before randomization. Brain imaging and 24 hour cardiac monitoring must have been repeated if new symptoms of stroke/TIA occurred after the initial stroke evaluation, as does 24-hour cardiac monitoring if symptoms suggestive of AF occur.

- Acute infectious disease
- Inflammatory disease, including rheumatic disease

2. Criterion Modified per Amendment INT-3

2.1. Criterion Modified per Amendment INT-5

2.2. The subject must be at increased risk for VTE by the total modified IMPROVE VTE Risk Score (Table 1; modified from Spyropoulos[37]) assessed at screening and verified at randomization.

a. If the total modified IMPROVE VTE Risk Score is ≥4, the subject meets this inclusion criterion.

b. If the total modified IMPROVE VTE Risk Score is 2 or 3, a D-dimer >2X ULN must have been obtained after the beginning of the index hospitalization and before randomization

Table 1: Modified IMPROVE VTE Risk Score

VTE Risk Factor	VTE Risk Score
Previous VTE	3
Known thrombophilia[a]	2
Current lower limb paralysis or paresis[b]	2
History of cancer[c]	2
ICU/CCU stay	1
Complete immobilization[d] ≥ 1 day	1
Age ≥60 years	1

CCU= cardiac care unit; ICU= intensive care unit; VTE= venous thromboembolism.
a: A congenital or acquired condition leading to excess risk of thrombosis (eg, factor V Leiden, lupus anticoagulant, factor C or factor S deficiency).
b: Leg falls to bed by 5 seconds, but has some effort against gravity (taken from NIH stroke scale).[25]
c: Cancer (excluding non-melanoma skin cancer) present at any time in the last 5 years (cancer must be in remission to meet eligibility criteria)
d: Immobilization is being confined to bed or chair with or without bath-room privileges.

3. Criterion Modified per Amendment INT-3

3.1. Life expectancy of at least 3 months.

4. Criterion modified per Amendment INT-3

4.1. Criterion modified per Amendment INT-5

4.2. Criterion modified per Amendment INT-6

4.3. Prescribed thromboprophylaxis (according to ACCP guidelines)[20] with UFH or LMWH (eg, dalteparin and enoxaparin) not exceeding 15000 U on any given day for UFH and not exceeding 5000 U on any given day for LMWH.

Table 2 below provides the minimum number of doses required by index hospitalization duration. For ischemic stroke with thrombolysis, do not use the index hospital duration

to determine the number of doses required. Instead, use the number of days the patient was in the hospital after the first day the patient was prescribed thromboprophylaxis.

Table 2: Minimum Number of Heparin Doses Required for Study Eligibility by Duration of Index Hospitalization

Index Hospitalization Duration (days)	LMWH doses required	UFH doses required
3	2	3
4	2	4
5	3	6
6	4	7
7	4	8
8	5	10
9	6	11
10	6	12

LMWH= low molecular weight heparin, UFH= unfractionated heparin.

Note: In the event that both LMWH and UFH are used during the index hospitalization, the number of doses of LMWH received should be doubled and added to the number of UFH doses received, and the UFH doses required column should be used to determine whether the requirement was met.

5. Criteria deleted per Amendment INT-3
6. Criterion modified per Amendment INT-3

6.1. Each subject must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study.

4.2. Exclusion Criteria

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

Bleeding Risk-Related Criteria

1. Criterion Modified per Amendment INT-5

1.1. Any bleeding (defined as bleeding requiring hospitalization, transfusion, surgical intervention, invasive procedures, occurring in a critical anatomical site, or causing disability) within 3 months prior to randomization or occurring during index hospitalization.

2. Criterion Modified per Amendment INT-3

2.1. Criterion Modified per Amendment INT-4
2.2. Criterion Modified per Amendment INT-5

2.3. Major surgery, biopsy of a parenchymal organ, ophthalmic surgery (excluding cataract surgery), or serious trauma (including head trauma) within 4 weeks before randomization.

Investigator discretion should be applied, but the following guidance may be considered for the purpose of this study.

***Major surgery** often involves opening 1 of the major body cavities the abdomen, the chest, or the skull and can stress vital organs. Major surgery usually is done using general anesthesia in a hospital operating room by a surgeon(s) and usually requires a stay of at least 1 night in the hospital after surgery.*

*In contrast, with **minor surgery**, major body cavities are not opened. Minor surgery can involve the use of local, regional, or general anesthesia and may be done in an emergency department, an ambulatory surgical center, or a doctor's office. Vital organs usually are not stressed, and surgery can be done by a single doctor, who may or may not be a surgeon. Usually, the person can return home on the same day that minor surgery is done.*

*Investigator discretion should be applied, but fracture or concussion would be considered **serious head trauma**, while external trauma without fracture or concussion could be considered for inclusion.*

3. Criterion Modified per Amendment INT-3
   3.1. Criterion Modified per Amendment INT-4
   3.2. Criterion Modified per Amendment INT-5
   3.3. Any planned major surgery (see exclusion criterion #2.3) or major invasive diagnostic procedure intended during the duration of the trial.

4. Criterion Modified per Amendment INT-3
   4.1. Subjects with any known coagulopathy or bleeding diathesis, or an INR >1.5 during the index hospitalization without a subsequent value (the last value before randomization) that is ≤ 1.5.

5. Criterion Modified per Amendment INT-3
   5.1. Criterion Modified per Amendment INT-5
   5.2. A history of hemorrhagic stroke or any intracranial bleeding at any time in the past, evidence of primary intracranial hemorrhage on CT or magnetic resonance imaging scan of the brain, or clinical presentation consistent with intracranial hemorrhage. This applies as well to subjects hospitalized for ischemic stroke upon randomization.

   Subjects with hemorrhagic transformation of an ischemic infarct prior to randomization are not excluded unless there is evidence of parenchymal hemorrhage (types PH-1 and PH-2):

   Hemorrhagic infarction type 1 (HI-1) is defined as small petechiae along the margins of the infarct, and HI type 2 (HI-2) is defined as more confluent petechiae within the infarcted area but without space-occupying effect. PH type 1 (PH-1) is defined as hematoma in ≤30% of the infarcted area with some slight space-occupying effect; PH type 2 (PH-2) is defined as dense hematoma >30% of the infarcted area with substantial space-occupying effect or as any hemorrhagic lesion outside the infarcted area (Berger, 2001[2]).

   Hemorrhagic infarction type 1 and HI-2 subjects are NOT excluded from this study, but PH-1 and PH-2 subjects ARE excluded from this study.

6. Criterion Modified per Amendment INT-3
   6.1. Criterion deleted per Amendment INT-5

7. Criterion Modified per Amendment INT-5

7.1. Subject has a history of or current intracranial neoplasm (benign or malignant), cerebral metastases, arteriovenous (AV) malformation, or aneurysm.

8. Active gastroduodenal ulcer, defined as diagnosed within 3 months or currently symptomatic or known AV malformations of the gastrointestinal tract.

9. Criterion Modified per Amendment INT-3

9.1. Screening platelet count <75 x 10^9 cells/L.

Concomitant Conditions or Diseases

10. Criterion Modified per Amendment INT-3

10.1. Criterion Modified per Amendment INT-5

10.2. Active cancer (excluding non-melanoma skin cancer) defined as cancer not in remission or requiring active chemotherapy or adjunctive therapies such as immunotherapy or radiotherapy. Chronic hormonal therapy (eg, tamoxifen, anastrazole, leuprolide acetate) for cancer in remission is allowed.

11. Criterion Modified per Amendment INT-3

11.1. Any medical condition (eg, atrial fibrillation) that requires use of any parenteral or oral anticoagulant(s) (eg, warfarin sodium or vitamin K antagonists, Factor II or Xa inhibitors, fibrinolytics) concomitantly with study medication.

12. Criterion Modified per Amendment INT-3

12.1. Bilateral and unilateral above-knee lower extremity amputation.

13. Subject has known allergies, hypersensitivity, or intolerance to rivaroxaban or any of its excipients.

14. Criterion Modified per Amendment INT-3

14.1. Severe renal insufficiency (baseline CrCl <30 mL/min calculated using the Cockcroft-Gault [6] formula provided in Section 9.1.2).

15. Criterion Modified per Amendment INT-3

15.1. Known significant liver disease (eg, acute hepatitis, chronic active hepatitis, cirrhosis) which is associated with coagulopathy or moderate or severe hepatic impairment.

16. Known HIV infection.

17. Sustained uncontrolled systolic blood pressure (BP) of ≥180 mmHg or diastolic BP of ≥100 mmHg at randomization despite treatment.

18. Criterion Modified per Amendment INT-3

18.1. Current drug or alcohol abuse, based on investigator's assessment.

19. Criterion Modified per Amendment INT-5

19.1. Cardiogenic or septic shock with the need for vasopressor(s) or devices for blood pressure support during index hospitalization.

20. Presence of inferior vena caval filter

21. Severe bronchiectasis or cavitary tuberculosis or any other pulmonary condition (eg, vasculitis) at risk for major hemoptysis

Drugs or Procedures

22. Criterion Modified per Amendment INT-3
22.1. Criterion Modified per Amendment INT-4
22.2.

a. Combined P-gp and strong CYP3A4 inhibitors (such as but not limited to ketoconazole, telithromycin or protease inhibitors) 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.

b. 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.

23. Criterion Modified per Amendment INT-3
23.1. Criterion Modified per Amendment INT-5
23.2. Received fibrinolysis during index hospitalization, unless received for ischemic stroke at least 3 full days before randomization.

24. Criterion Modified per Amendment INT-3
24.1. Criterion Modified per Amendment INT-5
24.2. Use of antiplatelet therapy during the index hospitalization, including:

a. ASA >162 mg/day

b. Clopidogrel >75 mg/day or ticlopidine >250 mg twice daily

c. Clopidogrel at any dose in combination with omeperazole or esomeprazole

d. Dipyridamole >400 mg/day

e. Cilostazol >200 mg/day

f. Dual therapy with 2 or more antiplatelet agents (dipyridamole with ASA is permitted)

g. Other P2Y12 receptor antagonists (eg, prasugrel, ticagrelor)

h. Thrombin-receptor antagonists (eg, vorapaxar)

25. Criterion Modified per Amendment INT-3
25.1. Childbearing potential without proper contraceptive measures, pregnancy or breast feeding.

a. Before randomization, a woman must be either:

- Not of childbearing potential: premenarchal; postmenopausal (>45 years of age with amenorrhea for at least 12 months or any age with amenorrhea for at least 6 months and a serum follicle stimulating hormone (FSH) level >40 IU/L]); permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral salpingectomy); or otherwise be incapable of pregnancy,

- Of childbearing potential and practicing a highly effective method of birth control consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies: eg, established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device or intrauterine system; barrier methods: condom with spermicidal foam/gel/film/cream/suppository or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; male partner sterilization (the vasectomized partner should be the sole partner for that subject); true abstinence (when this is in line with the preferred and usual lifestyle of the subject).

Note: If the childbearing potential changes after start of the study (eg, woman who is not heterosexually active becomes active, premenarchal woman experiences menarche) a woman must begin a highly effective method of birth control, as described above. The initiation of hormonal contraception for the purpose of the study is not recommended.

A woman of childbearing potential must have a negative serum (β human chorionic gonadotropin [β hCG]) or urine pregnancy test at screening.

b. A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a double-barrier method of birth control eg, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, and all men must also not donate sperm during the study, from the time of the first dose to the last dose of study drug.

26. Participation in another pharmacotherapeutic study or experimental medical device within 30 days before the start of study treatment.

27. Criterion deleted per Amendment INT-3
28. Criterion Modified per Amendment INT-3
    28.1. Criterion Modified per Amendment INT-5

    28.2. Prescribed daily use of nonsteroidal anti-inflammatory agents (NSAIDs) during the index hospitalization

29. Subject is unwilling or unable to complete all study visits as well as follow-up visit.
30. Subject is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.
31. Criterion deleted per Amendment INT-5

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's status changes (including laboratory results or receipt of additional medical records)

after screening but before randomization such that he or she no longer meets all eligibility criteria, the subject should not be randomized. But if the subject has been randomized, he/she should not be excluded from participation in the study and must be followed until the Day 75 (±5d) visit. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

Potential subjects 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 subjects require or take prohibited medications during the study as outlined below, they must either temporarily interrupt or permanently discontinue the study drug, as appropriate for the duration of the therapy with the prohibited medication:

1. Criterion Modified per Amendment INT-3
   1.1. Criterion deleted per Amendment INT-5
2. Criterion Modified per Amendment INT-3
   2.1. Criterion Modified per Amendment INT-4
   2.2. Combined P-gp and strong CYP3A4 inhibitors (such as but not limited to ketoconazole, telithromycin or protease inhibitors) 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.

3. Criterion Modified per Amendment INT-3
   3.1. Criterion Modified per Amendment INT-4
   3.2. 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.
4. Criterion Modified per Amendment INT-5

   4.1. Anticoagulant (eg, warfarin sodium or other vitamin K antagonists, Factor II or Xa inhibitors) is prohibited as concomitant therapy during the study. Study drug should be discontinued in subjects who develop any condition which requires anticoagulation or thromboprophylaxis (eg, atrial fibrillation, VTE) that will extend beyond the end of the study treatment phase.
5. Criterion deleted per Amendment INT-5
6. Criterion Modified per Amendment INT-5
   6.1. Fibrinolytic therapy (see Section 10.2.1 for guidance)
7. Criterion Modified per Amendment INT-5
   7.1. Use of antiplatelet therapy, including:
      a. ASA >162 mg/day
      b. Clopidogrel >75 mg/day or ticlopidine >250 mg twice daily
      c. Clopidogrel at any dose in combination with omeprazole or esomeprazole
      d. Dipyridamole >400 mg/day

e. Cilostazol >200 mg/day

f. Dual therapy with 2 or more antiplatelet agents (dipyridamole with ASA is permitted)

g. Other P2Y12 receptor antagonists (eg, prasugrel, ticagrelor)

h. Thrombin-receptor antagonists (eg, vorapaxar)

i. Prescribed daily non-steroidal anti-inflammatory drugs (temporary use as needed is allowed).

8. Criterion deleted per Amendment INT-5
9. Modification of an effective pre-existing therapy should not be made for the explicit purpose of entering a subject into the study.

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 drug, 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): Elliot Barnathan,MD, FACC

Institution: Janssen Research & Development

Signature: electronic signature appended at the end of the protocol Date: 31 March 2017

(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.

SIGNATURES

Signed by	Date	Justification
Elliot Barnathan	31Mar2017, 15:46:53 PM, UTC	Document Approval