Janssen Scientific Affairs, LLC *

Clinical Protocol

MulticEnter trial of Rivaroxaban for early disCharge of pUlmonaRY embolism from the Emergency Department (MERCURY PE)

Protocol 39039039APE4001; Phase 4

JNJ-39039039; BAY 59-7939 (rivaroxaban)

* Rivaroxaban (JNJ-39039039, BAY-59-7939) is being codeveloped under a collaboration and license agreement between Bayer HealthCare AG (BHC) and Ortho McNeil Pharmaceuticals, Inc (OMP) dated October 1, 2005. As determined by the parties, both BHC and Janssen Pharmaceuticals Inc (successor in interest to OMP) may use affiliated corporate entities to conduct this clinical trial. With regard to Janssen Pharmaceuticals Inc, such affiliates may include Janssen Research & Development, LLC (formerly Johnson & Johnson Pharmaceutical Research & Development LLC), Janssen Scientific Affairs, LLC, and Janssen-Cilag International NV. The term "sponsor" or "designee" is used throughout the protocol to represent these various legal entities that have been identified to perform various clinical trial services; the actual sponsor or designee is identified on the Contact Information page that accompanies this protocol.

This compound is approved for marketing in 6 indications in the United States.

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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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SYNOPSIS

MulticEnter trial of Rivaroxaban for early disCharge of pUlmonaRY embolism from the Emergency Department (MERCURY PE)

Rivaroxaban (JNJ-39039039; BAY 59-7939) is an oral anticoagulant. The mechanism of action of rivaroxaban is to selectively and to directly inhibit Factor Xa, which plays a central role in the cascade of blood coagulation by mediating thrombin formation. Rivaroxaban does not require metabolic conversion or a cofactor to exert its activity.

Rivaroxaban is marketed under the trade name XARELTO® and has been approved for multiple indications worldwide, including deep vein thrombosis (DVT) and pulmonary embolism (PE). In recent years, the ability to rapidly and to accurately stratify patients with PE according to their risk of clinical deterioration has gained importance and there is evidence that patients at low risk of clinical deterioration may be eligible for outpatient treatment with oral anticoagulants. The primary objective of this study is to determine if patients diagnosed with PE and identified as being at low risk of clinical deterioration may be safely discharged from the Emergency Department (ED) and treated with rivaroxaban as outpatients.

OBJECTIVE AND HYPOTHESIS

Primary Objective

The primary objective of the study is to demonstrate that low risk PE patients who are discharged from the ED to the home environment and treated with rivaroxaban as outpatients have fewer total days in the hospital for bleeding and/or venous thromboembolism (VTE) events through Day 30 compared to patients who are treated with initial hospitalization and standard-of-care.

Secondary Objective

The secondary objective of the study is to assess the reoccurrence of symptomatic, objectively confirmed VTE, defined as recurrent PE or new or recurrent DVT (including symptomatic upper extremity DVT) or VTE related death within 90 days of randomization.

Exploratory Objective

The exploratory objective of this study is to evaluate patient outcomes by baseline risk factors

Hypothesis

Clinical:

The clinical hypothesis is that an early discharge strategy for low risk PE patients, identified in the ED, and discharged to the home environment and treated with rivaroxaban as outpatients will result in fewer days in the hospital for bleeding and/or VTE events through Day 30 than patients treated with standard-of-care.

Safety:

The safety hypothesis is that major bleeding rates as assessed by the International Society on Thrombosis and Haemostasis (ISTH) criteria at 90 days of randomized treatment will be similar between the rivaroxaban and standard-of-care strategies.

OVERVIEW OF STUDY DESIGN

This is a randomized, open-label, parallel-group, multicenter study conducted in the United States (US). Eligible subjects will include men and women, 18 years of age and older, who have a confirmed diagnosis of acute symptomatic PE with or without symptomatic DVT. Approximately 300 PE subjects presenting to the ED and assessed as being at low risk of clinical deterioration using the Hestia criteria will be randomized in a 1:1 ratio to one of two treatment strategies: 1) rivaroxaban and discharge from the ED to the home environment or 2) standard-of-care (as per local protocol and defined by the medical team caring for the subject). All subjects will be followed for 90 days after starting randomized treatment. Subjects meeting all inclusion and no exclusion criteria will be eligible for enrollment.

The Hestia criteria are predefined validated clinical criteria that can be used to identify subjects with PE who are at low risk for subsequent clinical deterioration and who are candidates for anticoagulant treatment on an outpatient basis.

The study consists of a Screening and Randomization Period, followed by a 90-day open-label treatment period, and an end-of-study/early withdrawal (EOS) visit. The duration of study participation for each subject is approximately 3 months.

Subjects will undergo screening in the ED and must be randomized-within 12 hours after the confirmation of PE diagnosis. All bleeding events (ISTH major and clinically relevant non-major bleeding events), efficacy events (VTE related death, recurrence of PE or new or recurrent DVT) and all deaths during the study will be adjudicated in a blinded manner by a Clinical Endpoints Committee (CEC). Events will be adjudicated throughout the entire 90 days of randomized treatment. The CEC will independently review clinical events data as they become available, and will adjudicate and will classify deaths, bleeding events, and recurrence of PE and new or recurrent DVT in a consistent and unbiased manner.

An independent Data Monitoring Committee (DMC) will monitor the progress of the study and will ensure the safety of study subjects. An Executive Committee will be established and will review recommendations from the DMC regarding safety analyses and/or study modifications and will oversee implementation, if necessary, of these study modifications. In addition a Study Coordinator Operational Committee will be established to provide input to the operational logistics regarding study design and conduct of the study.

The frequency and timing of efficacy, safety, and other measurements are provided in the Time and Events Schedule.

SUBJECT POPULATION

Eligible subjects are men or women, 18 years of age or older, who present to the ED and have a confirmed diagnosis of an acute symptomatic PE with or without symptomatic DVT and who are deemed to be at low risk of clinical deterioration as determined by the Hestia criteria. PE diagnosis is expected to be confirmed per local standard-of-care with imaging techniques such as Computed Tomography, Pulmonary Angiography or Pulmonary Ventilation/Perfusion scan.

DOSAGE AND ADMINISTRATION

Subjects will be randomly assigned to 1 of 2 treatment strategies in a 1:1 ratio:

- Rivaroxaban at an initial dose of 15 mg taken orally twice daily with food for the first 21 days followed by a dose of 20 mg taken orally once daily with food, at approximately the same time each day for approximately 69 days for a total treatment duration of 90 days.

OR

- Standard-of-care (per local protocol and defined by the medical team caring for the subject)

Missed Dose

If a dose of rivaroxaban is not taken at the scheduled time, administer the dose as soon as possible on the same day as follows:

- For subjects receiving 15 mg twice daily: The subject should take rivaroxaban immediately to ensure intake of 30 mg rivaroxaban per day. In this instance, two 15 mg tablets may be taken at once. The subject should continue with the 15 mg twice daily regimen on the following day.
- For subjects receiving 20 mg once daily: The subject should take the missed rivaroxaban dose immediately.

EFFICACY EVALUATIONS/ENDPOINTS

Primary Endpoint

The primary clinical endpoint is the number of days of initial inpatient hospitalization (beginning from randomization to discharge from the hospital) plus any subsequent hospitalization(s) related to bleeding and/or VTE events up to 30 days.

Secondary Endpoints

- Reoccurrence of symptomatic, objectively confirmed VTE, defined as recurrent PE or new or recurrent DVT (including symptomatic upper extremity DVT) or VTE related death within 90 days of randomization.
- Number of unplanned hospital or physician office visits for VTE symptoms and/or bleeding through 90 days.
- Length of initial and subsequent hospitalization(s) for any reason through Day 90.
- Patient-reported outcomes will be captured at Day 7 for Site-of-Care Satisfaction and on Days 14, 30, and 90 for Anti-Clot Treatment Scale.
- Length of initial and subsequent hospitalizations as well as, VTE related re-hospitalization(s) due to recurrence will be economically evaluated.

EXPLORATORY EVALUATIONS

Outcomes by baseline risk factors will be evaluated.

BIOMARKER EVALUATIONS

A blood sample for biomarkers will be collected at screening from all subjects who give their consent for this blood sample. Biomarker samples will be used for research related to rivaroxaban, analysis of molecules involved in the clotting pathway, study comedications, and/or PE. They may also be used to develop tests/assays related to rivaroxaban, study comedications, or PE.

Patient-Reported Outcomes

Treatment and Site-of-Care satisfaction will be assessed. At follow-up visits Day 14, Day 30, and Day 90 treatment satisfaction will be assessed using a validated measure for treatment satisfaction: the ACTS.

The Satisfaction to Site-of-Care questionnaire (standard-of-care versus early discharge on rivaroxaban therapy) will be administered after 7 days on anticoagulant therapy.

The ACTS is comprised of two 2 subscales: Burdens (12 items) and Benefits (3 items). The treatment experience scores range from ‘Not at all’ to ‘Extremely’ on a five-point Likert scale (psychometric rating); higher scores indicate greater satisfaction with treatment.

Satisfaction to Site-of-Care (hospitalization versus home care) rates the patient's level of satisfaction to care and location with care received as well as preference to location of care provided. Patients rate the three 3 items of this scale of 1=Very satisfied; 2=Quite satisfied; 3=Neither; 4=Quite dissatisfied; and 5=Very dissatisfied for satisfaction questions and for the one preference question responses include 1=In the hospital; 2=In the community; and 3=No preference. This satisfaction scale will be administered after one 1 week on anticoagulant therapy. Statistical testing generating p values will be calculated for comparisons of hospital care and home care.

Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data, associated with medical encounters, will be collected in the eCRF by the investigator and study-site personnel for all subjects throughout the study. Length of initial and subsequent hospitalizations as well as, all-cause and VTE related re-hospitalizations due to recurrence will be economically evaluated.

SAFETY EVALUATIONS/ENDPOINTS

Safety Evaluations

All bleeding events will be captured as an Adverse Event of special interest.

- Primary safety: ISTH major bleeding
- Secondary safety: Clinically relevant non-major bleeding

Primary Safety Endpoint

The primary safety endpoint is ISTH major bleeding at Day 90.

Secondary Safety Endpoints

The secondary safety endpoints are VTE related death within 90 days of randomization and overall safety defined as a composite of ISTH major bleeding, clinically relevant non-major bleeding, and mortality.

STATISTICAL METHODS

Following pragmatic considerations, the sample size for this study was determined using assumptions related to the expected number of days of initial inpatient hospitalization (beginning from randomization to discharge from the hospital) and any subsequent hospitalization(s) related to bleeding and/or VTE events up to 30 days. A large-sample confidence interval (CI) approach was used to determine the sample size required for estimating the difference in mean length of stay between the two randomized groups. From Aujesky et al. 2011; the standard deviation is 1 day for the outpatient group and 3.1 days for the inpatient group from the initial hospital stay. From the available data, the average number of days of hospitalization after discharge is less than 2 days and the percentage of patients with VTE related hospitalization is less than 5%. With this information, the contribution from VTE related hospitalization after discharge has a very small impact on the standard deviations received from the initial hospital stays which were used in the sample size calculation. A total of a 150 subjects per group will provide a two-sided 95% CI with about a 0.5 day of margin of error. The margin of error is defined as the quantity from the observed difference in means to the end point of the CI.

The above sample size estimate will also allow an examination of the difference in the recurrence of VTE events in the 2 randomized groups. The incidence of recurrent VTE events is generally low and largely infrequent among low-risk PE patients. In the Aujesky et al. 2011 study, the 90-day recurrence rates of VTE among both inpatients and outpatients were reported to be less than 1% (with a 95% upper confidence limit = 2.7%).

TIME AND EVENTS SCHEDULE

Phase						
Period	Visit 1 Screening and Randomization[a]	Phone call Follow up #1	Phone call Follow up #2	Phone call Follow up #3	Visit 2	End of Study/Early Termination Visit 3[b]
Day	0/1	3 (± 1 day)	7 (± 2 days)	14 (± 2 days)	30 (-5) days	90 ± 5 days
Study Procedure						
Screening/Administrative						
PE Diagnosis/confirmation[c]	X					
Informed consent (ICF)	X					
Inclusion/exclusion criteria	X					
Medical history and demographics	X					
ED anticoagulant therapy (if applicable)	X[d]					
Pregnancy test	X[e]					
Physical examination[f]	X					
Vital signs[g]	X					
12-lead ECG[h]	X					
Height and Weight	X					
Study Drug Administration						
Randomization	X					
Dispensation/administration of study drug	X				X	
Drug accountability[i]		X	X	X	X	X
Safety Assessments						
ISTH major bleeding	X	X	X	X	X	X
Clinically relevant non-major bleeding events	X	X	X	X	X	X
Clinical Events						
VTE related death	X	X	X	X	X	X
Recurrence of PE or new or recurrent DVT	X	X	X	X	X	X
PRO Assessments						
ACTS[j].				X	X	X
Satisfaction to Site-of-Care[k]			X			
Clinical Laboratory Assessments (Blood samples)						
CrCl[l]	X					
Troponin	X					
Biomarker sample[m]	X					

Phase						
Period	Visit 1 Screening and Randomization[a]	Phone call Follow up #1	Phone call Follow up #2	Phone call Follow up #3	Visit 2	End of Study/Early Termination Visit 3[b]
Day	0/1	3 (± 1 day)	7 (± 2 days)	14 (± 2 days)	30 (-5) days	90 ± 5 days
Study Procedure						
Ongoing Subject Review						
Concomitant therapy[n]	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X

a) Subjects must be randomized within 12 hours after confirmation of PE diagnosis in the ED

b) The end of study visit will be performed at one of the following timepoints: at the completion of the open-label treatment with study drug Day 90 (± 5 days), or as soon as possible after a subject permanently discontinues study drug. For subjects who discontinue study drug prior to Day 90 (± 5 days), the site should make every effort to complete final study assessments. At a minimum, a final vital status (dead/alive) either by telephone or in person, or if applicable, by a review of the subject's medical record or available public records, unless this contact is not allowed by local regulation should be completed for all subjects who discontinue study drug prior to Day 90 (± 5 days).

c) PE diagnosis is expected to be confirmed per local standard-of-care with imaging techniques such as Computed Tomography, Pulmonary Angiography or V/Q scan.

d) A previous dose of VKA and or LMWH/UFH is allowed prior to randomization and must be recorded in the eCRF.

e) Women of childbearing potential must have a negative urine pregnancy test done locally at screening. Serum pregnancy testing may be performed if required by local regulation. 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.

f) The extent of the physical examination should be conducted by the site per usual local standard-of-care.

g) Vital signs include temperature, pulse/heart rate, respiratory rate, and blood pressure.

h) If blood sampling or vital sign measurement is scheduled for the same time point as electrocardiogram (ECG) recording, the procedures should be performed in the following order: ECG(s), vital signs, and blood draw.

i) Returned sponsor-supplied rivaroxaban will be counted at the in-person visits. Telephone calls should include a question regarding subject compliance with study drug.

j) The site will administer the ACTS by phone at Day 14(±2 days) ,and in person at the site at Day 30 (-5 days) and Day 90 (±5 days).

k) The site will administer the Satisfaction to Site-of-Care (hospitalization versus home care) questionnaire by phone at Day 7 of anticoagulant therapy (± 2 days).

l) CrCl to be conducted by the local laboratory using the Cockroft Gault formula using actual body weight. See Attachment 5

m) For all subjects who provide their consent for this sample an optional biomarker sample will be collected.

n) All medications, prescription and over the counter, including vitamins used within 14 days of the first dose of study drug and throughout the open-label treatment period of study drug must be recorded in the eCRF.

PE= pulmonary embolism; ICF= informed consent form; ED= emergency department; ECG= electrocardiogram; ISTH= International Society of Thrombosis and Haemostasis; V/Q= Pulmonary Ventilation/Perfusion ; VTE= venous thromboembolism; DVT= deep vein thrombosis; ACTS= Anti-Clot Treatment Scale; CrCl= serum creatinine; VKA= vitamin K antagonist; LMWH= low molecular weight heparin; UFH= unfractionated heparin; eCRF= electronic case report form.

ABBREVIATIONS

AE	Adverse Event
ACTS	Anti-Clot Treatment Scale
CEC	Clinical Endpoints Committee
eCRF	electronic case report form
CT	Computed Tomography
DMC	Data Monitoring Committee
DVT	deep vein thrombosis
EC	Executive Committee
ED	Emergency Department
ECG	electrocardiogram
EOS	end of study/early withdrawal
FXa	Factor Xa
eDC	electronic data capture
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
ISTH	International Society on Thrombosis & Haemostasis
LMWH	low molecular weight heparin
LOS	length of stay
NHAMCS	National Hospital Ambulatory Medical Care Survey
PE	pulmonary embolism
PESI	Pulmonary Embolism Severity Index
PQC	Product Quality Complaint
PRO	patient-reported outcome(s)
SC OC	Study Coordinator Operational Committee
UFH	unfractionated heparin
US	United States
VKA	vitamin K antagonists
VTE	venous thromboembolism

1. INTRODUCTION

Rivaroxaban (JNJ-39039039; BAY 59-7939) 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. As of 15 September 2014, over 84,000 subjects have been enrolled in interventional trials from Phase 1 through multiple large Phase 4 studies covering several indications and potential indications. Over 47,000 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 rivaroxaban, refer to the latest version of the Investigator's Brochure and Addenda for rivaroxaban.[14]

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 causing thrombosis. Venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE), represents one of the most common health problems in the United States (US). It is estimated that more than 2 million Americans develop an acute VTE event each year. In the European Union, incidence rates of DVT and PE are assumed to be slightly higher, but are generally consistent with those in the US. [10,27]

Deep vein thrombosis and PE are a burden for healthcare systems. They are associated with the potential for mortality and considerable morbidity in terms of recurrent events, post-thrombotic syndrome, and chronic thromboembolic pulmonary hypertension.[12,21,32] The treatment of DVT and PE aims at prevention of worsening of the existing thrombus, as well as prevention of recurrence of VTE[31] by the use of anticoagulants.

Historically, the only available oral anticoagulant was warfarin, an oral vitamin K antagonist (VKA). When first initiated, warfarin required 4 to 5 days to become effective and initial outpatient management was not possible as there would be an initial period where, despite proper warfarin dosing, there would be no functional anticoagulation. Therefore, for all patients requiring acute anticoagulation (eg, all new VTE diagnoses), hospitalization for intravenous anticoagulation bridging, until warfarin became effective, was the only option available. With the advent and availability of subcutaneously administered low molecular weight heparin (LMWH), a new option for bridging until warfarin became effective was possible. Theoretically, since intravenous therapy was no longer required, patients could avoid hospitalization by the self-injection of LMWH. Unfortunately, because of a lack of educational resources, a negative reimbursement structure, and general patient resistance to self-injection, the use of LMWH to avoid initial hospitalization for VTE therapy was generally poorly adopted in the US.

PE is a common diagnosis in the Emergency Department (ED); it is estimated that approximately 142,000 ED patients are diagnosed annually.[13] The risk of mortality and other serious side effects secondary to PE differs greatly according to underlying risk factors. While patients presenting with shock may experience a short-term mortality in excess of 30%[17,25] patients assessed to be at low risk have a reported mortality of less than 1%.[1,33] Patients with PE deemed to be at low risk are typically defined as patients who are hemodynamically stable without hypoxia, have no evidence of right heart strain or myocardial necrosis as evidenced by a normal troponin, and have a low risk of short-term mortality of less than 1%.[1,26,33] If anticoagulation bridging was unnecessary, this latter cohort could be potential candidates for outpatient treatment.

The advantages of avoiding hospitalization by outpatient treatment are numerous. Unnecessary hospitalization in and of itself represents an avoidable risk of adverse events.

Not only is there an advantage to avoiding hospitalization, but also the costs of a several day admission is significant. It is estimated that the average cost of a single inpatient PE therapy visit is $14,000.[9] Multiplied by the annual 142,000 ED PE diagnoses this equates to nearly 2 billion in expenditures.[7] It should be obvious that a large savings could be realized if an outpatient management strategy was used in only a very small percentage of selected PE patients.

Previous studies with LMWH and VKA have suggested that patients with PE who are at low risk of adverse events may be safely and effectively treated with anticoagulation therapy on an outpatient basis instead of being admitted to the hospital.[1,4,33] A recent systematic review and meta-analysis suggests that outpatient management of low risk PE is both feasible and safe as measured by low event rates at both 14 days and 3 months of follow up.[22]

1.1.1. Compound Profile

Rivaroxaban is an oral, direct, FXa inhibitor anticoagulant. Rivaroxaban is rapidly absorbed after oral administration, with peak plasma concentrations occurring approximately 2- to 4-hour postdose. 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 is approved for the treatment of several thrombosis mediated conditions. The clinical development program for rivaroxaban is extensive with over 84,000 subjects having been studied in interventional trials from Phase 1 through multiple large Phase 4 studies covering several indications and potential indications. Rivaroxaban is marketed under trade name XARELTO.

1.1.2. Efficacy and Safety Profile Based on Clinical Studies

The efficacy and safety of rivaroxaban has been studied in several large clinical development programs for the prevention and treatment of multiple thrombosis-mediated conditions including prevention of VTE in subjects undergoing major orthopedic surgery as well as acute treatment of DVT and or PE.

A pooled analysis of 4 studies comprising the RECORD program involving 12,729 subjects undergoing hip or knee arthroplasty demonstrated that rivaroxaban given at a dose of 10 mg once daily compared with enoxaparin given at a dose of 30 mg twice daily or 40 mg once daily significantly reduced the risk of symptomatic VTE and mortality (odds ratio: 0.48; 95% confidence interval [CI]: 0.30 to 0.76), without increasing the risk of major or clinically relevant non-major bleeding (odds ratio: 1.17; 95% CI: 0.93 to 1.46).[30]

The EINSTEIN program evaluated the use of rivaroxaban alone for anticoagulant therapy for the treatment and prevention of acute DVT and PE. The program consisted of 3 separate but related studies in over 9,447 subjects assessing the safety and efficacy of rivaroxaban for the treatment of acute symptomatic DVT (EINSTEIN-DVT), treatment of acute symptomatic PE (EINSTEIN-PE), and long-term prevention of VTE (EINSTEIN-Extension).

The EINSTEIN-DVT study included 3,449 subjects with acute symptomatic DVT without symptomatic PE and demonstrated that rivaroxaban (15 mg twice daily for 3 weeks followed by 20 mg once daily) was non-inferior to initial treatment with LMWH followed by warfarin (International Normalized Ratio [INR] 2.0 to 3.0). The risk of VTE reoccurrence with rivaroxaban was 2.1% versus 3.0% observed with enoxaparin/VKA (hazard ratio 0.68; 95% CI: 0.44 to 1.04). The rate of major and non-major clinically relevant bleeding was the same in both groups (8.1%).

The EINSTEIN PE study is the largest single-agent study ever conducted for the treatment of symptomatic PE.[8] In this multicenter, randomized, open-label, non-inferiority study, 4,832 subjects with confirmed acute symptomatic PE with or without symptomatic DVT were recruited. Subjects were treated for a period of 3, 6, or 12 months (based on a clinical evaluation of individual risk for recurrent thrombosis and bleeding) with either rivaroxaban 15 mg twice daily for the first 3 weeks followed by 20 mg once daily thereafter, or the standard approach of enoxaparin 1 mg/kg twice daily transitioning to a VKA (INR of 2.0 to 3.0) started no later than 48 hours after randomization. Rivaroxaban was non-inferior to enoxaparin/VKA for the primary efficacy endpoint of recurrent symptomatic VTE (fatal plus non-fatal PE and/or DVT; 2.1% versus 1.8%, P=0.003 for non-inferiority). The principal safety outcome of major plus non-major clinically relevant bleeding occurred with a similar incidence in both study arms, but major bleeding occurred significantly less frequently among subjects treated with rivaroxaban as compared to the enoxaparin/VKA group (1.1% versus 2.2% respectively, P = 0.003).

The EINSTEIN extension study (n=1,196 subjects) evaluated if extended duration of rivaroxaban administration (20 mg taken once daily or 6 to 12 months) in subjects who had previously completed 6 to 12 months of anticoagulation therapy including rivaroxaban and VKA was superior to placebo with respect to the rate of recurrent VTE. VTE recurred in 1.3% of the rivaroxaban-treated subjects versus 7.1% of the placebo-treated subjects ($p \leq 0.001$ for superiority). There was no significant difference for the principal safety endpoint of major bleeding (0.7% in the rivaroxaban versus 0% in placebo subjects, p=0.112).

The safety profile of rivaroxaban has been well established. As expected for a compound in the anticoagulant class of drugs, a bleeding risk is associated with the use of rivaroxaban. For the most comprehensive description of the safety profile of rivaroxaban, refer to the latest version of the Investigator's Brochure for rivaroxaban.[14]

1.2. Overall Rationale for the Study

In recent years, the ability to rapidly and to accurately stratify patients with PE according to their risk of clinical deterioration has gained importance.[2,3,14,33] Multiple clinical prognostic models have been developed and tested to identify low risk PE patients who may be candidates for outpatient care or for early discharge after an abbreviated in hospital stay. Collectively, these studies indicate that low risk PE patients may be prospectively identified. The most well validated prospective risk stratification is the Hestia criteria and Pulmonary Embolism Severity Index (PESI) scoring system (Table 1 and Table 2).These tools identify a cohort with a very low risk for bleeding and recurrent thrombosis and may be able to identify a population of PE patients who can be safely treated on an outpatient basis.[1,22]

Table 1 Hestia Exclusion Criteria for Outpatient Treatment

Is the patient hemodynamically unstable?[a]	Yes	No
Is thrombolysis or embolectomy necessary?	Yes	No
Active bleeding or high risk of bleeding?[b]	Yes	No
More than 24 h of oxygen supply to maintain oxygen saturation >90%?	Yes	No
Is pulmonary embolism diagnosed during anticoagulant treatment?	Yes	No
Severe pain needing intravenous pain medication for more than 24 h (infection, malignancy, no support system)?	Yes	No
Does the patient have a creatinine clearance of <30 ml/min?[c]	Yes	No
Does the patient have severe liver impairment?[d]	Yes	No
Is the patient pregnant?	Yes	No
Does the patient have a documented history of heparin-induced thrombocytopenia?	Yes	No
If the answer to one of the questions is 'yes', the patient cannot be treated at home		

[a] Include the following criteria, but leave these to the discretion of the investigator: systolic blood pressure <100 mmHg with heart rate > 100 beats/min; condition requiring admission to an intensive care unit.
[b] Gastrointestinal bleeding in the preceding 14 days, recent stroke (<4 weeks ago), recent operation (< 2 weeks ago), bleeding disorder or thrombocytopenia (platelet count <75 x 10^9 L^{-1}), uncontrolled hypertension (systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg
[c] Calculated creatinine clearance according to the Cockroft-Gault formula
[d] Left to the discretion of the investigator

Table 2 Original and Simplified Pulmonary Embolism Severity Index (PESI)		
Variable	Original PESI[a] Score	Simplified PESI[b] Score
Age >80 years	Age in years	1
Male sex	+10	-
History of cancer	+30	1
History of heart failure	+10	1[c]
History of chronic lung disease	+10	
Pulse ≥ 110 beats/minute	+20	1
Systolic blood pressure < 100 mm Hg	+30	1
Respiratory rate ≥ 30 breaths/minute	+20	-
Temperature < 36°C	+20	-
Altered mental status[d]	+60	-
Arterial oxygen saturation <90%[e]	+20	1

[a] A total point score for a given patient is obtained by summing the patient's age in years and the points for each applicable prognostic variable. The five following risk classes are defined based on patients' total point score: class 1 (≤65 points), class II (65-85 points), class III (86-105 points), class IV (106-125 points), and class V (>125 points). Patients in risk classes I/II are considered low risk.

[b] A total point score for a given patient is obtained by summing the points for each applicable prognostic variable. Patients with 0 points are considered low risk.

[c] The variables were combined into a single category of chronic cardiopulmonary disease.

[d] Altered mental status was defined as disorientation, lethargy, stupor, or coma.

[e] Arterial oxygen saturation was defined with and without the administration of supplemental oxygen.

While the exact number of PE patients who are very low risk candidates for early discharge is unknown, a recent review of the National Hospital Ambulatory Medical Care Survey (NHAMCS; a nationally representative weighted sampling of U.S. ED visits) evaluated adult patients with a primary diagnosis of PE.[23] It is suggested that a large early discharge of the PE candidate population may exist. In this analysis of 625 million US hospital visits from 2006 to 2010, an estimated 394,000 admissions were for PE. Due to the medications required during this time (heparin bridging to warfarin therapy), few PE cases were discharged from the ED and overall admission rates were extremely high (90%). However, only 16% of patients required treatment in an intensive care unit, a fact which demonstrated no significant changes over time. This suggests that the overwhelming majority of PE cases were cared for on a regular hospital floor in a monitored environment, a location which, except for the addition of monitoring and providing IV therapy (as required for heparin bridging), provides little additional care for the low risk PE patient.

The recent availability of rapid onset oral anticoagulants now creates a scenario where multiple days of hospitalization for anticoagulation to take effect are unnecessary. To determine the relative size of the cohort of candidate patients that potentially can be managed in an outpatient environment, Singer A, et al, applied the PESI score to the NHAMCS database.[24] The results demonstrated that overall 161,540 (41%) patients had a very low (13%, n=51,220) or low (28%, n=110,320) score. As low and very low PESI score correlates with mortality rates below 1%, this suggests that if an appropriate, safe, and effective therapy was available, nearly half of PE patients could receive initial treatment in the ED with a rapid onset oral anticoagulant and then be discharged directly from the ED, thus avoiding the risks and expense of in-hospital therapy.

Rivaroxaban, a rapid onset oral FXa inhibitor, has been shown to be a safe and effective treatment for PE. In the randomized, blinded, standard therapy controlled, 4,832 patient EINSTEIN PE study, patients were randomized to either standard therapy (bridging and warfarin) or rivaroxaban. Overall, 3,136 (64.9%) received therapy within 24 hours of hospitalization, with the rivaroxaban group having similar outcomes as the standard therapy cohort, despite the absence of a bridging period. These data strongly support the consideration that early treatment and discharge from the ED could safely avoid the unnecessary hospitalization of low-risk patients with PE.

Further, unlike warfarin, which is associated with coagulation parameter monitoring and dose adjustment difficulties; rivaroxaban does not require routine monitoring of coagulation parameters making it a more convenient option than warfarin.[23] These properties of rivaroxaban may enhance the option of outpatient treatment for PE patients.[5,8,19,33]

The proposed MERCURY PE study is designed to evaluate the number of days of hospitalization (from enrollment up to 30 days) as well as overall safety of low risk PE patients discharged from the ED to the home environment and treated with rivaroxaban as outpatients as compared to those treated with standard-of-care. Patients with PE who are at low risk for adverse outcomes, as defined by a Hestia score of zero, and who are candidates for treatment with anticoagulants including LMWH or any other approved new oral anticoagulant on an outpatient basis will be randomized to open label early ED discharge on rivaroxaban or standard therapy.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

Primary Objective

The primary objective of the study is to demonstrate that low risk PE patients who are discharged from the ED to the home environment and treated with rivaroxaban as outpatients have fewer total days in the hospital for bleeding and/or VTE events through Day 30 compared to patients who are treated with initial hospitalization and standard-of-care.

Secondary Objective

The secondary objective of the study is to assess the reoccurrence of symptomatic, objectively confirmed VTE, defined as recurrent PE or new or recurrent DVT (including symptomatic upper extremity DVT) or VTE related death within 90 days of randomization.

Exploratory Objective

The exploratory objective of this study is to evaluate patient outcomes by baseline risk factors.

2.2. Hypothesis

Clinical:

The clinical hypothesis is that an early discharge strategy for low risk PE patients, identified in the ED, and discharged to the home environment and treated with rivaroxaban as outpatients will result in fewer days in the hospital for bleeding and/or VTE events through Day 30 than patients treated with standard-of-care.

Safety:

The safety hypothesis is that major bleeding rates as assessed by the International Society on Thrombosis and Haemostasis (ISTH) criteria at 90 days of randomized treatment will be similar between the rivaroxaban and standard-of-care strategies.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a randomized, open-label, parallel-group, multicenter study conducted in the US. Eligible subjects will include men and women, 18 years of age and older, who have a confirmed diagnosis of acute, symptomatic PE with or without symptomatic DVT. Approximately 300 PE subjects presenting to the ED and assessed as being at low risk of clinical deterioration using the Hestia criteria will be randomized in a 1:1 ratio to one of two treatment strategies: 1) rivaroxaban and discharge from the ED to the home environment or 2) standard-of-care (as per local protocol and defined by the medical team caring for the subject). All subjects will be followed for 90 days after starting randomized treatment. Subjects meeting all inclusion and no exclusion criteria will be eligible for enrollment.

The Hestia criteria are predefined, validated clinical criteria that can be used to identify patients with PE who are at low risk for subsequent clinical deterioration and who are candidates for anticoagulant treatment on an outpatient basis.

The study consists of a Screening and Randomization Period, followed by a 90-day open-label treatment period, and an end of study/early withdrawal (EOS) visit. The duration of study participation for each subject is approximately 3 months.

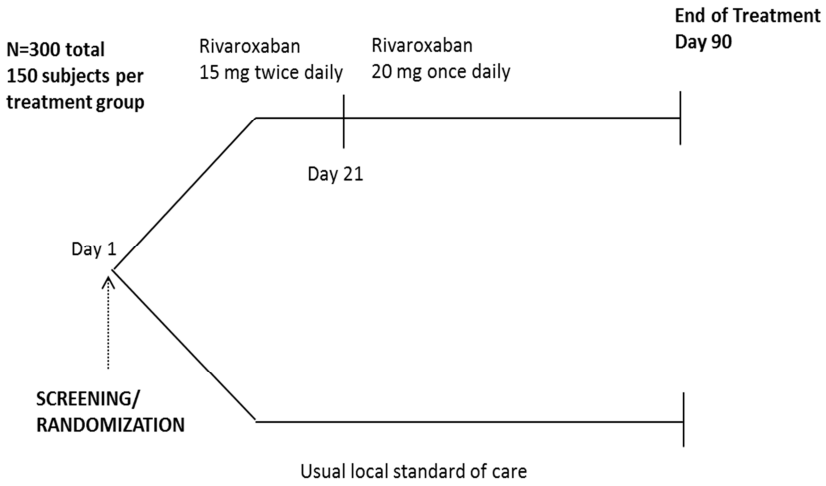
Subjects will undergo screening in the ED and must be randomized within 12 hours after confirmation of PE diagnosis. All bleeding events (ISTH major and clinically relevant non- major bleeding events) and efficacy events (VTE related death, recurrence of PE or new or recurrent DVT) and all deaths during the study will be adjudicated in a blinded manner by a Clinical Endpoints Committee (CEC). Events will be adjudicated throughout the entire 90 days of randomized treatment. The CEC will independently review clinical events data as they become available, and will adjudicate and will classify deaths, bleeding events, and recurrence of PE and new or recurrent DVT in a consistent and unbiased manner.

An Independent Data Monitoring Committee (DMC), an Executive Committee (EC) and Study Coordinator Operational Committee (SC OC) will be commissioned for this study. The DMC will monitor the progress of the study and will periodically review safety data. The DMC will follow guidelines specified in the DMC charter to ensure timely completion of planned and routine safety data reviews and analyses of the accumulating study data at prespecified time(s) and prepare its recommendations accordingly. The EC will review recommendations from the DMC regarding safety analyses and/or study modifications and will oversee implementation, if necessary, of these study modifications. The SC OC will provide input to the operational logistics regarding study design and conduct of the study. Additional information is provided in Section 11.5, Committees.

The frequency and timing of efficacy, safety, and other measurements are provided in the Time and Events Schedule.

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

Figure 1: Study Diagram: Clinical Protocol 39039039APE4001



3.2. Study Design Rationale

Study Population

The study population includes subjects with acute symptomatic PE with or without symptomatic DVT who are deemed to be at low risk of subsequent clinical deterioration.

The exclusion criteria selected are derived from the Hestia study, a prospective cohort study conducted in 12 hospitals in The Netherlands between 2008 and 2010. The objective of the Hestia study was to confirm the results of several small observational cohort studies in a large study, and to demonstrate that the incidences of VTE recurrence, major bleeding, and mortality are very low in patients selected for outpatient treatment with a simple set of exclusion criteria. The Hestia study population included patients with objectively proven acute PE who were triaged with the predefined criteria for eligibility for outpatient treatment, with LMWH (nadroparin) followed by VKA. Patients were deemed eligible for outpatient treatment if they

answered no to each of the exclusion criteria listed under exclusion criteria #1 (see Section 4.2) of this protocol. All patients eligible for outpatient treatment were sent home either immediately or within 24 hours after a PE was objectively diagnosed. Outpatient treatment was evaluated with respect to recurrent VTE, including PE or DVT, major hemorrhage and mortality during 3 months of follow-up. Patients meeting the following inclusion criteria, were potentially eligible: over 18 years of age with objectively proven acute PE presenting to the ED or outpatient clinic. Patients with asymptomatic or chronic PE, defined as duration of symptoms lasting for longer than 14 days and no acute worsening within the last 14 days, were not eligible for enrollment. The Hestia study population experienced a 2% rate of VTE reoccurrence, a 1% rate of all-cause mortality, and a 0.7% rate of major bleeding by day 90. These data suggest that the low-risk PE patients prospectively identified using the Hestia inclusion criteria can be safely treated on an outpatient basis as demonstrated by low rates of VTE recurrence, mortality, and bleeding.[33]

Rivaroxaban Dosage

The selected dose in this study is approved for the treatment of DVT and/or PE and for the reduction in the risk of recurrence of DVT and of PE. Rivaroxaban will be administered per the United States Package Insert at an initial dose of 15 mg taken orally twice daily with food for the first 21 days followed by a dose of 20 mg taken orally once daily with food, at approximately the same time each day for approximately 69 days for a total duration of 90 days.

Missed Dose

If a dose of rivaroxaban is not taken at the scheduled time, administer the dose as soon as possible on the same day as follows:

- For subjects receiving 15 mg twice daily: The subject should take rivaroxaban immediately to ensure intake of 30 mg rivaroxaban per day. In this instance, two 15 mg tablets may be taken at once. The subject should continue with the 15 mg twice daily regimen on the following day.
- For subjects receiving 20 mg once daily: The subject should take the missed rivaroxaban dose immediately.

Patient-Reported Outcome

The Anti-Clot Treatment Scale (ACTS) is a validated measure of patient treatment satisfaction that focuses on all aspects of anticoagulant treatment, both positive and negative. As part of the EINSTEIN DVT study, patients reported greater satisfaction in the rivaroxaban group compared with the enoxaparin/VKA group as demonstrated by ACTS Burdens and ACTS Benefits.[5] The improved scores seen with rivaroxaban treatment consistently across both tests provide further and more general support to the anticoagulation-specific effects seen with the ACTS scores alone.

As part of the EINSTEIN PE study, 2,397 patients in 7 countries were asked to complete the ACTS throughout the duration of treatment of up to 12 months.[23] Therefore, in both the EINSTEIN PE and EINSTEIN DVT patient satisfaction substudies, increases in ACTS Burdens scores with rivaroxaban were more pronounced over time compared with ACTS Benefits scores. The lower treatment burden may reflect the convenience offered by rivaroxaban compared with standard dual-drug therapy, including few drug interactions, a lack of dietary restrictions and no requirement for regular coagulation monitoring. Given that reduced treatment burden and regimen complexity are associated with better compliance, the reduced burden and monotherapy approach associated with rivaroxaban may contribute to increasing patient adherence to anticoagulant treatment, thereby improving clinical efficacy and outcomes in VTE patients.[23]

The Site-of-Care questionnaire is based on literature findings evaluating the location of care, ie, home versus hospital. This questionnaire assesses the patients' satisfaction and preference to location of care received, as well as their overall satisfaction with the care provided.

Open-Label, Randomized Design

An open-label study design is appropriate as blinding is not practical under the proposed study design, nor is it necessary when the main goal of the study is to evaluate treatment strategies in low-risk PE patients. The clinical and safety events in this study will be evaluated and appropriately adjudicated by a blinded CEC panel.

Randomization will be used to minimize bias in the assignment of subjects to treatment strategies and to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment strategies.

Rationale for Duration of Therapy

The projected duration of 90 days of subject exposure to study drug was selected for low risk PE patients per the CHEST guideline panel. In a prospective observational study of 1,180 inpatients categorized by a predefined risk assessment model, hospitalized patients were categorized as either low or high risk for VTE. Attending physicians were not notified of their patients' risk categories and patients were followed for symptomatic VTE for 90 days.[16] Thus, the duration of the treatment period for this study was selected to be long enough to evaluate the extent to which rivaroxaban can safely prevent VTE events in this selected study population. This approach will ensure an adequate number of events in order to perform a robust primary analysis and draw definitive conclusions relating to the primary hypothesis.

Safety Assessments

Rivaroxaban has been evaluated in studies that include over 84,000 subjects in Phase 1 through multiple large Phase 4 clinical trials of the rivaroxaban clinical development program. The adverse event profile of rivaroxaban has been well described and experience relative to the safe conduct of clinical trials is extensive. For example, over 12,000 subjects participated in the published Phase 3 RECORD studies of primary VTE prevention in subjects undergoing elective total hip/knee replacement alone. Additional characterization of the adverse event profile of

rivaroxaban will be possible using data from the EINSTEIN-DVT, EINSTEIN-PE, and EINSTEIN-Extension trials.

Given the extensive background of existing safety data, only serious adverse events (SAE), adverse events leading to discontinuation of study drug, and adverse events of particular concern to the investigator (see Sections 9.5, Safety Evaluations and 12.1, Adverse Events Definitions) will be collected in this study.

Biomarker Collection

A blood sample for biomarkers will be collected at screening from all subjects who give their consent for this blood sample. Biomarker samples will be used for research related to rivaroxaban, analysis of molecules involved in the clotting pathway, study comedications, and/or PE. They may also be used to develop tests/assays related to rivaroxaban, study comedications or PE.

Medical Resource Utilization and Health Economics

Treatment of the anticoagulant disease state in patients with acute PE with rivaroxaban versus inpatient hospitalization and local standard-of-care may result in lower length of stay (LOS) and unscheduled visits; therefore comparisons will be done across treatment strategies. Length of initial and subsequent hospitalizations as well as all-cause and VTE related re-hospitalizations due to recurrence will be economically evaluated.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed in the ED. Subjects will be assessed to be at low risk for clinical deterioration in the ED and should be randomized within 12 hours after confirmation of PE diagnosis.

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.

For a discussion of the statistical considerations of subject selection, refer to Section 11.2, Sample Size Determination.

4.1. Inclusion Criteria

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

1. Be a man or woman ≥18 years of age.

2. Have confirmed acute symptomatic PE with or without symptomatic DVT.

3. Be a PE patient diagnosed in the ED who is deemed to be at low risk of clinical deterioration as determined by the Hestia criteria.

   Note: Pulmonary embolism diagnosis is defined as the acute onset of dyspnea, chest pain, dizziness, tachycardia, and/or palpitations confirmed per local standard-of-care with imaging techniques such as Computed Tomography (CT), Pulmonary Angiography, or Pulmonary Ventilation/Perfusion scan.

4. Have no contraindications to and be able to complete randomized treatment and all study assessments.

5. Be able to be randomized within 12 hours after confirmation of PE diagnosis and be assessed as able to be discharged from the ED after the initiation of randomized therapy.

6. Before randomization, a woman must be either:

   - Not of childbearing potential: premenarchal; postmenopausal (>45 years of age with amenorrhea for at least 12 months; permanently sterilized (eg, bilateral tubal occlusion [which includes tubal ligation procedures as consistent with local regulations], hysterectomy, bilateral salpingectomy, bilateral oophorectomy); 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.

7. A woman of childbearing potential must have a negative urine pregnancy test at screening. Serum pregnancy testing may be performed if required by local regulation.

8. Subject must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

9. Subject must have a life expectancy of at least 6 months.

10. 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 are 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. The subject will be excluded if he or she:

1. Answers YES to any of the Hestia criteria questions below:

    - Include the following criteria but left to the discretion of the investigator: Hemodynamically unstable as determined by the following: systolic blood pressure <100 mm Hg with heart rate >100 bpm; condition requiring admission to an intensive care unit.
    - Thrombolysis or embolectomy necessary.
    - Active bleeding or high risk for bleeding as determined by the following: gastrointestinal bleeding in the preceding 14 days, recent stroke (less than 4 weeks ago) recent operation (less than 2 weeks ago), bleeding disorder or thrombocytopenia (platelet <75,000 at screening), uncontrolled hypertension (systolic >180 mm Hg or diastolic >110 mm Hg at screening).
    - Oxygen supply to maintain oxygen saturation > 90% >24 hours.
    - Pulmonary embolism diagnosed during anticoagulant treatment.
    - Intravenous pain medication >24 hours.
    - Medical or social reason for treatment in the hospital >24 hrs
    - Creatinine clearance of less than 30 mL/min(calculated using the Cockroft Gault formula using actual body weight) at screening. (See Attachment 5)
    - Severe liver impairment; left to the discretion of the investigator
    - Pregnant
    - Documented history of heparin-induced thrombocytopenia

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 within 7 days before randomization or planned use during the study.

3. 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. Has contraindications to the use of any anticoagulant therapy (eg, bleeding diathesis, history of gastrointestinal bleeding within 1 year or coagulopathy documented at screening).

5. Has known allergies, hypersensitivity, or intolerance to rivaroxaban or its excipients (refer to Investigator's Brochure).[14]

6. Has a history of malignancy within 1 year before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence). Actively receiving treatment for cancer or patients undergoing treatment for cancer or palliative care or CT evidence suggesting undiagnosed malignancy.

7. Has elevated troponin levels at screening ≥99th percentile for normal control patients.

8. Has received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 30 days before the planned first dose of study drug.

9. Has taken any disallowed therapies as noted in Section 8, Pre-study and Concomitant Therapy before the planned first dose of study drug.

10. Is a woman who is pregnant, or breast-feeding, or planning to become pregnant.

11. Has any barriers to treatment adherence or follow up (ie. alcohol abuse, illicit drug use, psychosis, dementia). Patients with insufficient social support for outpatient treatment, which will include patients unlikely to have successful follow up (homeless and prisoners) are not eligible for participation.

12. Has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

13. Had major surgery, (eg, requiring general anesthesia) within 14 days before screening, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study.

    Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate.

14. 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.

15. Has a history of human immunodeficiency virus (HIV) antibody positive, or tests positive for HIV at screening.

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 the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. 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:

1. Non-steroid anti-inflammatory drugs and antiplatelet agents are discouraged, however, non-steroidal anti-inflammatory drugs – for occasional use only (defined as less than 2 weeks of daily dosing) are allowed.

2. Dual aspirin and clopidogrel therapy is prohibited.

3. A woman of childbearing potential who is heterosexually active must remain on a highly effective method of birth control (see inclusion criteria).

Refer to Section 8 Prestudy and Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Procedures for Randomization and Stratification

The principle purpose of randomization is to ensure unbiased treatment assignment in a manner that assures minimum allocation bias, and balancing both known and unknown prognostic factors at the baseline. Subjects will be randomly assigned in a 1:1 ratio to the outpatient group to receive rivaroxaban or to the inpatient group to receive standard-of-care. The treatment assignment is based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by study centers.

Blinding

As this is an open label study, blinding procedures are not applicable.

6. DOSAGE AND ADMINISTRATION

Subjects will be randomly assigned to 1 of 2 treatment strategies in a 1:1 ratio:

- Rivaroxaban at an initial dose of 15 mg taken orally twice daily with food for the first 21 days followed by a dose of 20 mg taken orally once daily with food, at approximately the same time each day for approximately 69 days for a total treatment duration of 90 days.
  - The first rivaroxaban dose should be administered in the ED as soon as possible after randomization.
  - If the patient has received prerandomization anticoagulant therapy:
    - Rivaroxaban should be planned 4 hours after the bolus injection or stopping the infusion with unfractionated heparin (UFH) or within 6 to 12 hours after the last injection of LMWH with a twice-daily regimen, or within 12 to 24 hours after the last injection of LMWH with a once-daily regimen, or 12 to 24 hours after last injection of fondaparinux.

OR

- Standard-of-care (per local protocol and defined by the medical team caring for the subject)

Missed Dose

If a dose of rivaroxaban is not taken at the scheduled time, administer the dose as soon as possible on the same day as follows:

- For subjects receiving 15 mg twice daily: The subject should take rivaroxaban immediately to ensure intake of 30 mg rivaroxaban per day. In this instance, two 15 mg tablets may be taken at once. The subject should continue with the regular 15 mg twice daily regimen as recommended on the following day.
- For subjects receiving 20 mg once daily: The subject should take the missed rivaroxaban dose immediately.

Transition from Study Drug to Other Therapy at the End of Study

The decision of how best to manage the patient after the end of this study will be made by the clinical investigator and the patient's physician (See Attachment 2).

Study-site personnel will instruct subjects on how to store study drug for at-home use as indicated for this protocol. Rivaroxaban should be stored at room temperature. (See Section 14.4, Preparation, Handling, and Storage).

6.1. Temporary Discontinuation of Study Drug

If the investigator determines that anticoagulation must be temporarily discontinued to reduce the risk of bleeding with surgical or other procedures:

Rivaroxaban should be stopped at least 24 hours before the procedure to reduce the risk of bleeding. In deciding whether a procedure should be delayed until 24 hours after the last dose of rivaroxaban, the increased risk of bleeding should be weighed against the urgency of intervention. Rivaroxaban should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established, noting that the time to onset of therapeutic effect is short. If oral medication cannot be taken during or after surgical intervention, consider administering a parenteral anticoagulant.

Study drug should be temporarily discontinued if the subject:

- Experiences a major bleeding event. 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.
- Has a SAE 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).

Study drug can be resumed when the investigator considers it safe to do so. If more than 5 consecutive days of study drug is missed, the subject will permanently discontinue study drug and have end-of-treatment visit assessments performed (see Section 9.1.3, Open-Label Treatment Phase).

7. TREATMENT COMPLIANCE

Study drug will be self-administered by subjects; the number of study drug tablets dispensed will be recorded and compared with the number returned. Subjects will receive instructions on compliance with study drug administration at the randomization visit. During the course of the study, the investigator or designated study-site personnel will be responsible for providing additional instruction to reeducate any subject who is not compliant with taking the study drug. In addition, during the follow-up phone calls at Days 3, 7, and 14, the Study Coordinator will confirm that the standard-of-care patients have obtained their medications and that all patients, including those in the rivaroxaban group, are taking them as directed and have no questions.

Study personnel will maintain a log of all study drug dispensed. Drug supplies for each subject randomized to rivaroxaban will be inventoried and reconciled throughout the study. Subjects in the standard-of-care treatment strategy will be asked about treatment compliance throughout the study. Subjects should report any missed doses. The study personnel should discuss reasons for missed doses with subjects to ascertain if the missed dose was related to study endpoints or safety. It is understood that subjects may occasionally miss a dose or that a subject may be

placed on temporary discontinuation (see Section 6.1, Temporary Discontinuation of Study Drug). Any unexplained missed doses that result in the subject returning more than 20% of the prescribed study drug will be considered noncompliance. The investigator should contact the medical monitor to discuss any unexplained study drug non-compliance.

8. PRESTUDY AND CONCOMITANT THERAPY

Allowed Therapy

- A previous dose of VKA and/or LMWH/UFH is allowed prior to randomization.
- Antiplatelet agents are discouraged. However if indicated, aspirin up to a dose of 100 mg/day is allowed. Clopidogrel up to a dose of 75 mg/day or alternative P2Y12 inhibitors are allowed (Prasugrel 10 mg/day or ticagrelor 90 mg twice daily).

  Medicines that reduce gastric acid (eg, H2 antagonists or proton-pump inhibitors) may reduce the incidence of gastrointestinal bleeding in subjects who are treated with anticoagulants, and unless contraindicated, their use should be considered.

Prohibited Therapy

- Combined P-gp and strong CYP3A4 inhibitors (such as but not limited to ketoconazole, telithromycin or protease inhibitors) use is prohibited within 4 days before randomization, or during the study. Itraconazole use is prohibited within 7 days before randomization and during the study.
- Combined P-gp and strong CYP3A4 inducers (such as but not limited to rifampin/rifampicin, rifabutin, rifapentine, phenytoin, phenobarbital, carbamazepine, or St. John's Wort) use is prohibited within 2 weeks before randomization or during the study.
- Dual anti-platelet therapy is prohibited.

All prestudy therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements); administered up to 14 days before first dose of study drug must be recorded at screening.

All concomitant therapies administered at the time of an occurrence of an adverse event must be recorded in the electronic case report form (eCRF). Concomitant therapies should be recorded beyond EOS visit only in conjunction with SAEs that meet the criteria outlined in Section 12.3.2, Serious Adverse Events.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; different from the study drug must be recorded in the eCRF. Recorded information will include a description of the type of the drug, treatment period, dosing regimen, route of administration, and its indication. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a subject into the study.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule summarizes the frequency and timing of efficacy and safety measurements applicable to this study.

All visit-specific patient-reported outcome (PRO) assessments should be conducted before any tests, procedures, or other consultations for that visit to prevent influencing subject perceptions.

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.

The total blood volume for each subject in the study is approximately 6 mL for safety. Subjects who give consent to the collection of an optional biomarker sample will have an additional 10 mL drawn for a total blood volume of 16 mL.

Volume of Blood to be Collected From Each Subject

Type of Sample	Volume per Sample (mL)	No. of Samples per Subject	Total Volume of Blood (mL)[a]
CrCl	3.5	1	3.5
Troponin	2.5	1	2.5
Optional biomarker sample	10.0	1	10.0
Approximate Total	16.0		16.0

[a] Calculated as number of samples multiplied by amount of blood per sample.

The maximum amount of blood drawn from each subject in this study will not exceed 16 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1.2. Screening Phase

Screening may begin at any time after consent is obtained during the time the patient is in the ED. Subjects will be screened using local laboratory results for the inclusion and exclusion clinical laboratory parameters.

9.1.3. Open-Label Treatment Phase

Day 1/Day of Randomization

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be randomly assigned by an interactive web response system on Day 1 to 1 of 2 treatment strategies. Randomization must be performed while the subject is in the ED and within 12 hours after initial diagnosis of a PE.

Procedures Throughout Open-Label Treatment Phase

The study will include scheduled telephone calls and visits as outlined in the Time and Event Schedule. Visits by the subject to the site are permissible for management of therapy or for evaluation of adverse events. Patients randomized to the rivaroxaban treatment strategy may be treated as the investigator feels is appropriate, including primary care physician/cardiologist/pulmonologist referrals and any follow-up visits/calls as indicated. These interventions will be captured in the eCRF.

Blood samples for exploratory biomarker testing will be collected from those subjects who give permission for this sample; see Section 9.3, Biomarkers, for additional information.

End of Treatment/Early Termination

Subjects will have an end-of-treatment/early withdrawal visit at Day 90, or at the time of early treatment discontinuation or early withdrawal. At this visit, investigators must ensure that all subjects are started on adequate anticoagulation, as indicated, based upon local standards. Additional guidance is provided in Section 6.1, Temporary Discontinuation of Study Drug and Attachment 2.

Reasons for withdrawal from the study are presented in Section 10.2, Withdrawal From the Study. If a subject permanently withdraws before the end of the open-label treatment phase, he or she will have end-of-treatment/early withdrawal visit assessments performed as soon as possible and no more than 5 days after the last dose of study drug. For these subjects, this visit will serve as the last data collection point for endpoints in this study, with the exception of the patient's vital status at what would have been the time of study completion.

Subjects who do not complete the study will have their vital status and any bleeding or VTE related events collected at Day 90, either by telephone or in person, or if applicable, by a review of the subject's medical record or available public records, unless this contact is not allowed by local regulations.

9.2. Efficacy

9.2.1. Evaluations

Local standards of VTE diagnosis are acceptable in patients who are symptomatic for VTE. Such radiologic procedures for PE diagnosis include CT, Pulmonary Angiography, catheter pulmonary angiogram, and lung ventilation / perfusion lung scan. Symptomatic DVT may be diagnosed by ultrasonography or venography.

All bleeding events (ISTH major and clinically relevant non-major bleeding events) and efficacy events (VTE related death, recurrence of PE or new or recurrent DVT) and all deaths during the study will be adjudicated in a blinded manner by a CEC; these events will be adjudicated throughout the entire 90 days of randomized treatment.

The following definitions will be applied by the CEC to confirm a suspected episode of recurrent PE/DVT:

Suspected (recurrent) PE with one of the following findings:

- a (new) intraluminal filling defect in segmental or more proximal branches on CT,
- a (new) intraluminal filling defect or an extension of an existing defect or a new sudden cut-off of vessels more than 2.5 mm in diameter on the pulmonary angiogram,
- a (new) perfusion defect of at least 75% of a segment with a local normal ventilation result (high-probability) on ventilation/perfusion lung scintigraphy.
- inconclusive CT, Pulmonary Angiography, or lung ventilation/perfusion scintigraphy –with demonstration of DVT in the lower extremities by compression ultrasound or venography.

Suspected (recurrent) DVT with one of the following findings if there were no previous DVT investigations:

- abnormal compression ultrasound
- an intraluminal filling defect on venography.

Suspected (recurrent) DVT with one of the following findings if there was a DVT investigation at screening:

- abnormal compression ultrasound where compression had been normal or, if non-compressible during screening, a substantial increase (4 mm or more) in diameter of the thrombus during full compression,
- proximal extension of an intraluminal filling defect, or a new intraluminal filling defect, or
- proximal extension of non-visualization of veins in the presence of a sudden cut-off on venography.

<u>All Deaths</u>

- PE based on objective diagnostic testing, autopsy, or death which cannot be attributed to a documented cause and for which PE/DVT cannot be ruled out (unexplained death).
- In the absence of objective testing, a suspected episode of DVT or PE will be considered as confirmed if it led to a change in anticoagulant treatment at therapeutic dosages for more than 2 days.

9.2.2. Endpoints

Primary Endpoint

Clinical

The primary clinical endpoint is the number of days of initial inpatient hospitalization (beginning from randomization to discharge from the hospital) plus any subsequent hospitalization(s) related to bleeding and/or VTE events up to 30 days.

Secondary Endpoints

- Reoccurrence of symptomatic, objectively confirmed VTE, defined as recurrent PE or new or recurrent DVT (including symptomatic upper extremity DVT) or VTE related death within 90 days of randomization.
- Number of unplanned hospital or physician office visits for VTE symptoms and/or bleeding through 90 days.
- Length of initial and subsequent hospitalization(s) for any reason through Day 90.
- Patient-reported outcomes will be captured at Day 7 for Site-of-Care Satisfaction and Days 14, 30, and 90 for ACTS.
- Length of initial and subsequent hospitalization(s) as well as, VTE related re-hospitalization(s) due to recurrence will be economically evaluated.

Exploratory Endpoint

Outcomes by baseline risk factors will be evaluated.

9.3. Biomarkers

A blood sample to evaluate troponin levels will be obtained at screening in order to determine study eligibility.

A blood sample will be collected for exploratory biomarker testing from all subjects who give permission for this sample. Subjects who consent to this optional blood sample collection will be asked to provide 1 blood sample which will be stored and used for validation of a biomarker assay.

9.4. Patient-Reported Outcomes

Treatment and Site-of-Care satisfaction will be assessed. At follow-up visits Day 14, Day 30, and Day 90 treatment satisfaction will be assessed using a validated measure for treatment satisfaction: the ACTS.

The Satisfaction to Site-of-Care questionnaire (standard-of-care versus early discharge on rivaroxaban therapy) will be administered after 7 days on anticoagulant therapy. (See Attachment 4)

The ACTS is comprised of 2 subscales: Burdens (12 items) and Benefits (3 items). The treatment experience scores range from ‘Not at all’ to ‘Extremely’ on a five-point Likert scale (psychometric rating); higher scores indicate greater satisfaction with treatment.

Satisfaction to Site-of-Care (hospitalization versus home care) rates the patient’s level of satisfaction to care and location with care received as well as preference to location of care provided. Patients rate the 3 items of this scale of 1=Very satisfied; 2=Quite satisfied; 3=Neither; 4=Quite dissatisfied; and 5=Very dissatisfied for satisfaction questions and for the one preference question responses include 1=In the hospital; 2=In the community; and 3=No preference. This satisfaction scale will be administered after 1 week on anticoagulant therapy.

Statistical testing generating p values will be calculated for comparisons of hospital care and home care.

Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data, associated with medical encounters, will be collected in the eCRF by the investigator and study-site personnel for all subjects throughout the study. Length of initial and subsequent hospitalizations as well as, all-cause and VTE related re-hospitalizations due to recurrence will be economically evaluated.

9.5. Safety Evaluations

The primary safety endpoint is ISTH major bleeding at Day 90.

The secondary safety endpoints are VTE related death within 90 days of randomization and overall safety defined as a composite of ISTH major bleeding, clinically relevant non-major bleeding, and mortality.

The study will include the following evaluations of safety according to the timepoints provided in the Time and Events Schedule:

All bleeding events will be captured as an Adverse Event (AE) of special interest

- Primary safety: ISTH major bleeding
- Secondary safety: Clinically relevant non-major bleeding

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

9.5.1. Bleeding Events

The study will use the ISTH Bleeding Event Classification Scale to assess bleeding events as major, clinically relevant non-major bleeding, or minimal bleeding. Similar to efficacy outcomes, the same independent CEC will adjudicate and will classify bleeding events according to definitions in the CEC charter.

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

An ISTH major bleeding event is defined as overt bleeding 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.

Clinically relevant non-major 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 clinically relevant non-major 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

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

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

9.5.2. 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

Results of clinical laboratory tests from the local laboratory will be used at the screening visit to confirm eligibility of potential subjects.

Separate laboratory tests will likely be part of the subjects' hospital evaluation, but are not required by the protocol. 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 hospitalization. Any laboratory test along with reference ranges relevant to a SAE 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 screening and randomization:

- Troponin
- Serum creatinine (CrCl to be calculated using Cockcroft-Gault formula (See Attachment 5)

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

Additional tests may be performed by the local laboratory as usual care, but these results will not be captured in the eCRF unless a result constitutes an AE/SAE.

Electrocardiogram

If blood sampling or vital sign measurement is scheduled for the same time point as electrocardiogram (ECG) recording, the procedures should be performed in the following order: ECG(s), vital signs, and blood draw.

Vital Signs: temperature, pulse/heart rate, respiratory rate, and blood pressure.

Physical Examination

The extent of the physical examination will be conducted by the site per usual local standard-of-care.

9.6. Sample Collection and Handling

The date and of sample collection must be recorded in the eCRF. If blood samples are collected via an indwelling cannula, an appropriate amount (1 mL) of serosanguineous 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 will 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

A subject will be considered to have completed the study if he or she has completed assessments at Day 90 of the open-label phase or has experienced a clinical endpoint that precludes further continuation in the study. Subjects who prematurely discontinue study treatment for any reason before completion of the open-label phase will not be considered to have completed the study.

10.2. Withdrawal From the Study

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

- Lost to follow-up
- Withdrawal of consent
- Death
- Noncompliance defined as any unexplained missed doses that result in the subject's returning more than 20% of the prescribed study drug. The investigator should contact the medical monitor to discuss any unexplained study drug non-compliance.
- Discontinuation of study treatment. A subject's study treatment will be discontinued if:
  - The investigator or sponsor believes (eg, that for safety or tolerability reasons such as an adverse event) it is in the best interest of the subject to discontinue treatment
  - The subject becomes pregnant

If a subject discontinues study treatment before the end of Day 90, end-of-treatment assessments should be obtained.

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

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. 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 from the study early, the end-of-treatment assessments should be obtained.

A vital status (alive/dead) should be completed on all randomized subjects who do not complete the study, regardless of the reason for discontinuation. This vital status should be completed at what would have been at Day 90 (±5 days). If the final study assessments are completed for an early discontinued subject at Day 90 time point, a vital status is not required.

Withdrawal From the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the ICF.

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 data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

11.1. Subject Information

Demographic data and baseline characteristics of all subjects will be summarized by treatment strategy. Summaries of continuous variables will include number of subjects, mean, median, minimum, maximum, and standard deviation. Summaries of categorical variables will include frequency and percentage of subjects in each category. Medical history data will be summarized by body system and will include frequency and percentages of subjects with each condition. Frequencies and percentages for subjects completing, discontinuing and reasons for discontinuations will be presented and summarized for all subjects combined and by each treatment strategy.

Analysis Sets

For the purpose of statistical analyses, 2 analysis populations will be considered:

- Intention-to-treat (ITT) analysis set: The intention to treat analysis set includes all subjects who are randomized into the study.

- Safety analysis set: The safety population includes all randomized subjects who take at least 1 dose of study drug.

11.2. Sample Size Determination

Following pragmatic considerations, the sample size in this study was determined using assumptions related to the expected number of days of initial inpatient hospitalization (beginning from randomization to discharge from the hospital) and any subsequent hospitalization(s) related to bleeding and/or VTE events up to 30 days. A large-sample CI approach was used to determine the sample size required for estimating the difference in mean LOS between the two randomized groups. From Aujesky et al. 2011, the standard deviation is 1 day for the outpatient group and 3.1 days for the inpatient group from the initial hospital stay. From the available data, the average days of hospitalization after discharge is less than 2 days and the percentage of patients with VTE related hospitalization is less than 5%.[4] With this information, the contribution from VTE related hospitalization after discharge has a very small impact on the standard deviations received from the initial hospital stay which were used in the sample size calculation. A total of 150 subjects per group will provide a two-sided 95% CI with about 0.5 day of margin of error.

The margin of error is defined as the quantity from the observed difference in means to the end point of the CI.

The above sample size estimate will also allow an examination of the difference in the recurrence of VTE events in the 2 randomized groups. The incidence of recurrent VTE events is generally low and largely infrequent among low-risk PE patients. In the Aujesky et al.2011 study, the 90-day recurrence rates of VTE among both inpatients and outpatients were reported to be less than 1% (with a 95% upper confidence limit=2.7%).[4]

11.3. Analyses for Primary and Secondary Endpoints

The primary and major secondary analyses will be based on the ITT analysis set.

Analysis for Primary Endpoint

The primary clinical endpoint is the LOS of hospitalization (for the standard-of-care and rivaroxaban groups) beginning from randomization through discharge from the ED plus any bleeding or VTE events through 30 days A two-sided 95% CI will be calculated for the difference in LOS for 2 treatment groups.

Analysis for Major Secondary Endpoints

A two-sided 95% CI will be calculated for the difference of reoccurrence of symptomatic, objectively confirmed VTE, defined as recurrent PE or new or recurrent DVT (including symptomatic upper extremity DVT) or VTE related death within 90 days of randomization. The same procedure may be applied to the reoccurrence of VTE at Day 7 and Day 30 when appropriate.

A two-sided 95% CI will be calculated for the difference of ISTH major bleeding and death at Day 90 and for the composite of ISTH major bleeding and mortality at Day 90 when appropriate.

The following data will be summarized: ISTH major and clinically relevant non-major bleeding, the total number of days alive and out of the hospital, medical contacts for any reason, including office and ED visits, number of unplanned hospital or physician office visits for VTE symptoms and/or bleeding.

Patient-reported outcomes will be captured and summarized at Day 7 for Site-of-Care Satisfaction and Days 14, 30, and 90 for ACTS.

11.4. Safety Analyses

Safety analyses will be based on the safety analysis set that includes all subjects who are randomized and take at least 1 dose of study drug.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities. All reported adverse events with onset during the treatment phase (ie, treatment-emergent adverse events [TEAEs], and adverse events that have worsened since baseline) will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a SAE.

TEAEs, using the Medical Dictionary for Regulatory Activities, will be summarized for each treatment group by body system, preferred term, intensity, and relationship to the study treatment. A TEAE is defined as any adverse event that occurred after randomization and after the first intake of study treatment or that started before the first intake of study treatment and worsened in intensity during the active treatment period. Subjects who experienced a SAE or who prematurely discontinued from the study due to an adverse event will be listed. For a large number of subjects discontinuing due to adverse events, the distributions of the time to treatment discontinuation due to an adverse event will be estimated by the Kaplan-Meier estimates.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at screening. A listing of subjects with any laboratory results outside the reference ranges will be provided. A listing of subjects with any markedly abnormal laboratory results will also be provided.

The clinical laboratory results at baseline will be summarized using descriptive statistics. The baseline is defined as the last measurement prior to the first dose of the randomized treatment.

Electrocardiogram

The effects on cardiovascular variables will be evaluated by means of descriptive statistics and frequency tabulations for baseline ECG.

Vital Signs

Descriptive statistics of temperature, pulse/heart rate, respiratory rate, and blood pressure (systolic and diastolic) resting values will be summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits will be summarized. The vital sign measures at screening will be summarized using descriptive statistics. The baseline is defined as the last measurement prior to the first dose of the randomized treatment.

Physical Examination

Abnormal findings from the physical examinations will be listed.

11.5. Committees

11.5.1. Executive Committee

An EC will oversee the conduct and reporting of the study. The members of the EC will be sponsor representatives identified by the study team and will include at least 2 clinical experts. Details will be provided in a separate EC charter.

11.5.2. Clinical Endpoint Committee

An independent blinded CEC will apply the protocol definitions and will adjudicate and classify the following endpoints: ISTH major bleeding, VTE related death and overall safety defined as a composite of ISTH major bleeding and mortality. The CEC will include leading scientific investigators with coagulation, diagnostic, and statistical expertise. All bleeding events (ISTH major and clinically relevant non-major bleeding events), efficacy events (VTE related death, recurrence of PE or new or recurrent DVT) and all deaths during the study will be adjudicated in a blinded manner by the CEC. Events will be adjudicated throughout the entire 90 days of randomized treatment. The CEC will independently review clinical events data as they become available, and will adjudicate and classify the specified events in a consistent and unbiased manner. Details will be provided in a separate CEC charter.

11.5.3. Data Monitoring Committee

The DMC will monitor the progress of the study and will periodically review safety data. After the review, the DMC will discuss any potential safety issues with the sponsor and will recommend to the EC any analyses or study modifications. The details will be provided in a separate DMC charter.

The DMC will consist of at least 1 medical expert in the relevant therapeutic area and at least 1 statistician.

11.5.4. Study Coordinator Operational Committee

A SC OC will provide input into the operational logistics of the study design and conduct for the MERCURY PE study. The committee will meet on a regular basis and will be composed of a minimum of 3 Study Coordinators who have expertise in conducting ED studies. The details will be provided in a separate SC OC charter.

12. ADVERSE EVENT REPORTING

Rivaroxaban has been extensively studied in Phase 1 through multiple large Phase 4 clinical studies involving over 84,000 patients, including over 47,000 patients exposed to rivaroxaban, and its overall safety profile has been well characterized. Appropriate information concerning adverse events were systematically collected and submitted to regulatory authorities. For the purposes of this study certain nonserious adverse events will not be collected, while certain events will be collected as endpoints and therefore not collected and reported as SAEs. All data on safety outcomes will be reviewed regularly by the DMC. This will be explained in Section 12.3.1, All Adverse Events.

Section 12.1.1, Adverse Event Definitions and Classifications describes the usual definitions of adverse events and serious adverse events.

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.

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 International Conference on Harmonisation [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 European Union Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The 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*

† Note: The standard-of-care group in this study will involve a hospital admission for anticoagulation therapy to treat the PE. This hospital admission for patients randomized to the standard-of-care group should not be reported as an SAE. However, if, during the course of the hospital stay, a patient in the standard-of-care group develops a reportable event, or has an event that prolongs the hospital stay beyond the expected duration that event should be reported as an SAE. If a patient in the standard-of-care group is admitted to the hospital, has an uneventful hospital stay and is discharged, no SAE should be reported.

All inpatient hospitalizations for patients randomized to the rivaroxaban/early discharge group and subsequent hospitalizations for patients randomized to the standard-of-care group should be reported as an SAE.

*Medical and scientific judgment should be exercised in deciding whether expedited (SAE) 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.

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. For a non-sponsor investigational medicinal product with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the package insert.

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, Attributes Definitions.

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 (SAE) 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
- Unexpected therapeutic or clinical benefit from use 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

Adverse Events and special reporting situations, as discussed in this section, whether serious or non-serious, will be reported from the time a 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 within 30 days after the last dose of study drug, 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.

Although not required, any nonserious adverse events, of particular concern to the investigator may be recorded in the eCRF to bring them to the attention of the sponsor. All other non-serious adverse events not fulfilling the above mentioned criteria will **not** be reported as adverse events in the eCRF. (See Attachment 1)

Given the extensive existing safety data associated with rivaroxaban, study endpoint events, or events that appear suggestive of study endpoint events, occurring from the time of randomization until the EOS will not reported as serious adverse events, regardless of seriousness or severity and final event assessment by the CEC, unless otherwise specified. These events will be captured on an event page in the eCRF. Any study endpoint events or events that appear suggestive of endpoint events occurring prior to randomization as well as other serious adverse events and adverse events leading to permanent discontinuation of the study drug will be collected as adverse events or serious adverse events in this study independent of the final CEC assessment. The following study endpoint events or events that appear suggestive of a study endpoint event have been identified for this study.

- Recurrent PE or new or recurrent DVT or VTE related event
- Bleeding events
  - Bleeding events requiring medical attention, and/or hospitalization will be entered on the AE page of the eCRF; any bleeding event leading to permanent study drug discontinuation will also be entered on the AE page of the eCRF.

The following adverse events or SAEs will be collected and entered into the eCRF. SAEs need to be reported to the sponsor within the appropriate timeline as described in Section 12.3.2, Serious Adverse Events.

- All deaths, regardless of cause, will be reported as an SAE
- Non-bleeding, adverse events leading to permanent study drug discontinuation
- Any SAE(s) that is not an endpoint event as listed above
- Common types of adverse reactions to drug therapy, including but not limited to the following, when severe in intensity, should be considered SAEs:

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

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number

The sponsor will provide the site with these study cards

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).

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)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- The standard-of-care group in this study will involve a hospital admission for anticoagulation therapy to treat the PE. This hospital admission for patients randomized to the standard-of-care group should not be reported as an SAE. However, if, during the course of the hospital stay, a patient in the standard-of-care group develops a reportable event or has an event that prolongs the hospital stay beyond the expected duration, that event should be reported as an SAE.
- All inpatient hospitalizations for patients randomized to the rivaroxaban/early discharge arm and subsequent hospitalizations for patients randomized to the standard-of-care group should be reported as an SAE.
- For the purposes of this study, endpoint events will not be considered SAEs, refer to Section 12.3.1 for details.
- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

Any death of a subject that was not due to a study endpoint within 30 days of the last dose of study drug, whether or not the event is expected or associated with the study drug, is considered a serious adverse event.

12.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects 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, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) 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.

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 rivaroxaban supplied for this study consists of 15 and 20 mg tablets. The 15 mg tablets are red, and the 20 mg tablets are dark red. It will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.

14.2. Packaging

The rivaroxaban study drug will be packaged in polypropylene blisters (the 15 and 20 mg starter pack dispensed at Randomization) and polyethylene bottles (the 20 mg tablets dispensed at Visit 2); both are 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

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

Refer to the pharmacy manual/study site investigational product manual for additional guidance on study drug preparation, handling, and storage.

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, 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, and study drug returned by the subject, 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, or used returned study drug for destruction, 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. Whenever a subject brings his or her study drug to the study site for pill count, this is not seen as a return of supplies. 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's Brochure
- Pharmacy manual/study site investigational product manual
- Patient-reported outcome questionnaires and user manual-for the ACTS questionnaire only. Refer to Attachment 3 and Attachment 4 for the PRO questionnaires.
- Interactive web response system manual
- Sample ICF

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.

The total blood volume to be collected is considered to be 6 ml. Subjects who agree to the optional biomarker sample will have an additional 10 mL drawn for a total blood volume of 16 mL.

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 Independent Ethics Committee (IEC) or Institutional Review Board (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 (if applicable, the notification will be submitted through the head of investigational institution).

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 ICFs must be signed before performance of any study-related activity. The ICFs that 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 choosing 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.

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.

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.

Exploratory biomarker research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. Long-Term Retention of Samples for Additional Future Research

Biomarker samples collected in this study may be stored for up to 10 years (or according to local regulations) for additional research. Samples will only be used to understand how rivaroxaban, impacts the anticoagulant disease state in patients with acute pulmonary embolism, analysis of molecules involved in the clotting process and the impact of concomitant medications used to treat PE. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.2, Withdrawal From the Study (Withdrawal From the Use of Samples in Future Research).

17. ADMINISTRATIVE REQUIREMENTS

17.1. Regulatory Documentation

17.1.1. 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.

17.1.2. Required Prestudy 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

17.2. 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.

17.3. 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, 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 required 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:

- Demographics, including race
- Temperature, respiratory rate, pulse/heart rate and blood pressure
- Height and weight
- Patient responses to the 2 PROs conducted by telephone

The minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- PE confirmation
- CrCl and troponin results conducted at screening

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

17.5. Case Report Form Completion

Case report forms are provided for each subject in 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 eCRF.

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

All subjective measurements (eg, PRO) will be completed by the same individual who made the initial baseline determinations whenever possible. The investigator must verify that all data entries in the eCRFs are accurate and correct.

All eCRF 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.

If corrections to a eCRF are needed after the initial entry into the eCRF, 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. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRFs 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 use on site monitoring for this study.

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. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRFs 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 eCRF 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.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the eCRF 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 visit 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 visit 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 eCRFs. 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 biomarker 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 eCRF data from all study sites that participated in the study into the sponsor's database. Results of biomarker 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 endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 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 Reporting of Study Endpoints, Adverse Drug Reactions, Adverse Events and Serious Adverse Events

	Study Endpoint	**Study drug Adverse Drug Reactions (ADRs) and AEs leading to permanent study drug discontinuance**		**Other Serious Adverse Events[a]**	**Any Other Adverse Events**	
	Recurrent PE or new or recurrent DVT or VTE related death Bleeding events that: Require medical attention, and/or hospitalization and any bleeding event leading to permanent study drug discontinuation ISTH major bleeding events Clinically relevant non-major bleeding events[b]	Common types of adverse reactions to drug therapy, including but not limited to the following events: Suspected toxic effect on the bone marrow including severe thrombocytopenia (platelet count less than 50,000/µL), severe neutropenia (white blood cell count less than 500 µL), pancytopenia, aplastic anemia Suspected hypersensitivity reaction (eg, anaphylaxis, angioedema, severe urticaria, bronchospasm, etc.) Severe skin reactions such as Stevens-Johnson Syndrome Suspected severe liver injury Non-bleeding AEs leading to permanent drug discontinuation		Any event meeting the SAE criteria that is not a study endpoint <u>All deaths should be reported as an SAE</u>	Any nonserious adverse event(s), of particular concern to the investigator	
Capture in eCRF?	Yes	Yes		Yes	Captured if the investigator would like to notify the sponsor of the event	
Capture as a SAE and report to Sponsor Safety Unit within 24 hours?[b]	No	Does it meet the criteria as a SAE?		Yes[a]	Does it meet the criteria as a SAE?	
		Yes	No		No[c]	No

[a] Within 24 hours of the investigational staff's knowledge of the event, the site should enter initial information in the eCRF regarding the event. Additional information should be recorded in the eCRF as soon as it becomes available.

[b] All bleeding events will be AEs of Special Interest.

Attachment 2 Switching to or From Rivaroxaban

PREMATURE DISCONTINUATION OF XARELTO INCREASES THE RISK OF THROMBOTIC EVENTS. Premature discontinuation of any oral anticoagulant, including XARELTO, increases the risk of thrombotic events. To reduce this risk, consider coverage with another anticoagulant if XARELTO is discontinued for a reason other than pathological bleeding or completion of a course of therapy.

In order to provide guidance on switching to or from rivaroxaban the following guidance from the prescribing information is provided:

VKA to Rivaroxaban

When switching patients from warfarin to rivaroxaban, discontinue warfarin and start rivaroxaban as soon as the INR is below 3.0 to avoid periods of inadequate anticoagulation.

Rivaroxaban to VKA

No clinical trial data are available to guide converting patients from rivaroxaban to warfarin. Rivaroxaban affects INR, so INR measurements made during co-administration with warfarin may not be useful for determining the appropriate dose of warfarin. One approach is to discontinue rivaroxaban and begin both a parenteral anticoagulant and warfarin at the time the next dose of rivaroxaban would have been taken.

Non-Warfarin Anticoagulant to Rivaroxaban

For patients currently receiving an anticoagulant other than warfarin, start rivaroxaban 0 to 2 hours prior to the next scheduled evening administration of the drug (low-molecular-weight heparin or non-warfarin oral anticoagulant) and omit the next regularly scheduled administration of the other anticoagulant. For unfractionated heparin being administered by continuous infusion, stop the infusion and start rivaroxaban at the same time.

Rivaroxaban to Non-Warfarin Anticoagulant

For patients currently taking rivaroxaban and transitioning to an anticoagulant with rapid onset, discontinue rivaroxaban and give the first dose of the other anticoagulant (oral or parenteral) at the time that the next rivaroxaban dose would have been taken.

Attachment 3 Anti-Clot Treatment Scale (ACTS) Questionnaire

We are interested in your experiences of anti-clot treatment. We would be grateful if you could help us by filling out this questionnaire. The questions below ask about your experiences of anti-clot treatment during the past 4 weeks. All of the information you provide is COMPLETELY CONFIDENTIAL. Please be sure to answer all questions.

INSTRUCTIONS: We are interested in your experiences of anti-clot treatment during the past 4 weeks. Please circle the number in the box that best describes your views.

During the past 4 weeks...	Not at all	A little	Moderately	Quite a bit	Extremely
How much does the possibility of bleeding as a result of your anti-clot treatment limit you from taking part in vigorous physical activities (e.g. exercise, sports, dancing, etc.)?	1	2	3	4	5
How much does the possibility of bleeding as a result of your anti-clot treatment limit you from taking part in your usual activities (e.g. work, shopping, housework etc.)?	1	2	3	4	5
How bothered are you by the possibility of bruising as a result of your anti-clot treatment?	1	2	3	4	5
How bothered are you by having to avoid other medicines (e.g. aspirin) as a result of your anti-clot treatment?	1	2	3	4	5
How much does your anti-clot treatment limit what you eat and drink (including alcohol)?	1	2	3	4	5
6. How much of a hassle (inconvenience) are the daily aspects of your anti-clot treatment (e.g. remembering to take your medicine at a certain time, taking the correct dose of your medicine, limiting what you eat and drink (including alcohol), etc.)?	1	2	3	4	5
7. How much of a hassle (inconvenience) are the occasional aspects of your anti-clot treatment (e.g. the need for blood tests, going to or contacting the hospital/doctor, making arrangements for treatment while travelling etc.)?	1	2	3	4	5

Now I want to ask you about daily and occasional aspects of your anti-clot treatment during the past 4 weeks…

	Not at all	A little	Moderately	Quite a bit	Extremely
8. How difficult is it to follow your anti-clot treatment?	1	2	3	4	5
9. How time-consuming is your anti-clot treatment?	1	2	3	4	5
10. How much do you worry about your anti-clot treatment?	1	2	3	4	5
11. How frustrating is your anti-clot treatment?	1	2	3	4	5
12. How much of a burden is your anti-clot treatment?	1	2	3	4	5
13. Overall, how much of a negative impact has your anti-clot treatment had on your life?	1	2	3	4	5
14. How confident are you that your anti-clot treatment will protect your health (e.g. prevent blood clots, stroke, heart attack, DVT, embolism)?	1	2	3	4	5
15. How reassured do you feel because of your anti-clot treatment?	1	2	3	4	5
16. How satisfied are you with your anti-clot treatment?	1	2	3	4	5
17. Overall, how much of a positive impact has your anti-clot treatment had on your life?	1	2	3	4	5

THANK YOU FOR YOUR HELP

Attachment 4 Site-of-Care Satisfaction Questionnaire

1. Overall how satisfied are you with the care you received? ❑ Very Satisfied ❑ Quite Satisfied ❑ Neither ❑ Quite Dissatisfied ❑ Very Dissatisfied
2. Overall how satisfied are you with the location of care you received? ❑ Very Satisfied ❑ Quite Satisfied ❑ Neither ❑ Quite Dissatisfied ❑ Very Dissatisfied
3. Do you think it is preferable to provide the kind of care you received? ❑ In the Hospital ❑ In the Community ❑ No Preference

Attachment 5 Cockcroft and Gault formulas

The creatinine clearance (expressed as mL/min), is yielded by the Cockcroft and Gault formulas, relating serum creatinine, with age (in years) and body weight (in kg). For this study, CrCl will be done by the local lab. The alternative formulas, based on µmol/L, are included below for your general reference only

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:

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

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

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): Hayes Dansky, MD

Institution: Janssen Scientific Affairs, LLC

Signature: [redacted] Date: 16 June 2015

(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.

LAST PAGE