Janssen Research & Development *

Clinical Protocol

A Randomized, Double-blind, Event-driven, Multicenter Study Comparing the Efficacy and Safety of Rivaroxaban with Placebo for Reducing the Risk of Death, Myocardial Infarction or Stroke in Subjects with Heart Failure and Significant Coronary Artery Disease Following an Episode of Decompensated Heart Failure

COMMANDER HF Study

Protocol RIVAROXHFA3001; Phase 3
BAY 59-7939/16302

Amendment INT-3

JNJ-39039039; BAY 59-7939 (rivaroxaban)

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This compound is approved for marketing in 5 indications.

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

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Prepared by:	Janssen Research & Development, LLC
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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	18 April 2013
Amendment INT-1	02 May 2014
Amendment INT-2	05 December 2014
Amendment INT-3	01 December 2016

Amendments are listed beginning with the most recent amendment.

Amendment INT-3 (01 December 2016)

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

The overall reason for the amendment is to revise the target number of primary efficacy endpoint events. The current COMMANDER trial data show a longer than planned enrollment period, a lower than anticipated primary efficacy event rate and a higher than anticipated study drug discontinuation rate: Recruitment of subjects in the COMMANDER HF (RIVAROXHFA3001) study has been slower than anticipated which has subsequently led to a longer double blind treatment phase (was approximately 30 months, now estimated to be 54 months). Moreover, a lower than initially estimated aggregate primary efficacy event rate (14% vs. a predicted 17%) and a higher than originally anticipated study drug discontinuation rate (13% vs. a predicted 10%) have been observed. The higher discontinuation rate combined with the longer study duration has resulted in a greater percentage of subjects being off treatment, diluting the potential treatment effect and thus reducing the study power (originally planned to be 90%). In order to better understand the implication of these findings, a blinded simulation study based on currently available trial data was performed and showed that an increase in the target number of primary efficacy endpoint events (the first occurrence of the composite of all cause death, MI or stroke) may be able to potentially counterbalance this problem and maintain the study power. Thus, the target number of primary efficacy endpoint events is revised from 984 to 1,200 for the final analysis, and the target number of primary efficacy endpoint events for the interim analysis is revised from approximately 500 to approximately 600.

Applicable Section(s)	Description of Change(s)
Rationale: To revise the target number of primary efficacy endpoint events from “984” to “1,200” based on a blinded simulation study as described above.	
Synopsis (Overview of Study Design); 3.1 Overview of Study Design; 3.2 Study Design Rationale.	Revised the number of primary efficacy endpoint events from “984” to “1,200”.
Synopsis (Sample Size Justification); 11.2 Sample Size Determination	Added the sentence “The study is revised to observe occurrences of the primary efficacy event in 1,200 unique randomized subjects based on a blinded simulation study performed on currently available trial data (ie, longer enrollment period, lower than anticipated primary efficacy event rate, higher than anticipated study drug discontinuation rate). Further details are described in the Statistical Analysis Plan (SAP).”
Rationale: To revise the target number of primary efficacy endpoint events from approximately “500” to approximately “600” for the interim analysis, to be consistent with the overall changes in the target number of primary efficacy endpoint events for the study.	

Applicable Section(s)	Description of Change(s)
11.2 Sample Size Determination; 11.3 Efficacy Analyses; 11.9 Interim Analysis.	Revised the number of primary efficacy endpoint events from approximately "500" to approximately "600"for the interim analysis.
Rationale: To change the estimated duration of the double-blind treatment phase and the average duration of a subject in the study, to reflect the overall slower than anticipated recruitment rate for the study.	
Synopsis(Overview of Study Design); 3.1 Overview of Study Design; 3.2 Study Design Rationale;	Changed the estimated duration of double-blind treatment phase from "6 to 30 months" to "6 to 54 months". Changed the estimated average duration of a subject in the study from approximately "16 months" to "29 months"
Rationale: To add a new prohibited therapy, ie, any medication that is contraindicated in patients with heart failure in the Prohibitions and Restrictions Section for safety reasons.	
4.3 Prohibitions and Restrictions (Criterion 5); 8 Prestudy and Concomitant Therapy (Prohibited Therapies).	Added a new prohibited therapy (under Criterion 5): "Any drug which is contraindicated in patients with heart failure (eg, cilastazol)"
Rationale: To change the stratification factor for the efficacy and safety analyses from "country" to "region" due to the increase in the number of enrolling countries and the corresponding smaller sample sizes expected in those countries.	
Synopsis (Analyses-Efficacy); 11.3 Efficacy Analyses;11.6 Safety Analyses; 11,9 Interim Analysis.	Changed the stratification by "country" to the stratification by "region" in the log-rank test for the primary efficacy analysis. Changed the stratification by "country" to the stratification by "region" in a Cox proportional hazards model.
Rationale: To add the log-rank test stratified by "country" as one of the sensitivity analyses in the statistical analyses plan.	
11.3 Efficacy Analyses.	Added the log-rank test stratified by country as one of the sensitivity analyses.
Rationale: To add additional subgroups/populations for the analyses.	
Synopsis (Analyses-Efficacy); 11.3 Efficacy Analyses.	Added "BNP, NT-proBNP (≤ median vs > median)" for subgroup analyses.
11.3 Efficacy Analyses.	Added the following sentence for sensitivity analyses: "Additional sensitivity analyses will also be conducted based on subject populations enrolled under various versions of the protocol amendments."
Rationale: To change the safety analyses from "study drug received" to "study drug assigned" based on the fact that the COMMANDER HF is a long term study and the incidence of a subject receiving the wrong study drug during the entire treatment period will be low. The statistical analysis plan may include sensitivity analyses of subjects according to study drug received, if needed.	

Applicable Section(s)	Description of Change(s)
11.6 Safety Analyses	Changed the sentence "Subjects will be analyzed according to study drug received" to "Subjects will be analyzed according to the study drug assigned". Deleted the sentence "If a subject receives both drugs, the subject will be analyzed as randomized."
Rationale: To add additional details for the safety analyses	
Synopsis (Analyses-Safety; 11.6 Safety Analyses	Added the sentence "In addition, summary statistics will be provided for all other reported bleeding events."
11.6 Safety Analyses	Added the sentence "The safety outcomes will also be analyzed for other observational periods as defined in the SAP."
Rationale: To delete a sentence describing the interim analysis that is no longer valid based on the blinded simulation study performed on currently available trial data.	
11.2 Sample Size Determination.	Deleted the sentence "The interim analysis will have ~75% power to detect an RRR of 30% in the primary efficacy endpoint."
Rationale: To provide additional clarification on the efficacy outcome events	
9.2.1 Efficacy Evaluations	Deleted "Transient ischemic attack (TIA)" from the evaluation list of outcome events. Added the sentence "Transient ischemic attack (TIA) is not an outcome event. The date of the TIA should be entered in the eCRF." Added the phrase "without any information regarding the immediate cause provided" under "Death with Unknown Cause"
9.5.1 Safety Evaluations; 12.3.1 All Adverse Events.	Clarified that "traumatic bleeding events resulting in death" are considered as non-cardiovascular (CV) Serious Adverse Events.
Rationale: To provide more clarity	
Synopsis (Overview of Study Design); 3.1 Overview of Study Design; 9.1.3 Double-Blind Treatment Phase; 10.2.2 Permanent Discontinuation of Study Treatment	Replaced the phrase "these subjects will be strongly encouraged to return for all scheduled visits" with the phrase "these subjects should return for all scheduled visits"
Synopsis (Overview of Study Design); 3.1 Overview of Study Design.	Replaced the phrase "study drug must be temporarily discontinued and an appropriate treatment for the event must be administered." with the phrase "study drug may be temporarily held if necessary or if using other anticoagulant drugs or thrombolytic therapy."
Synopsis (Overview of Study Design); 3.1 Overview of Study Design; 16.1 Study-Specific Design Considerations.	Added the following phrase (in italic) to the sentence "the investigator is asked to strongly encourage the subjects to allow regular contact *(eg, by telephone)*… "

Applicable Section(s)	Description of Change(s)
Synopsis (Overview of Study Design); 3.1 Overview of Study Design.	Added the following phrase (in italic) to the sentence "study medication must be permanently discontinued for any intracranial hemorrhage *or for any reason listed in Section 10.2.2*."
9.5.1 Safety Evaluations	Changed the sentence "Blood transfusion and products will be recorded" to "Transfusion with blood or blood products will be recorded"
9.1.1 Overview	Replaced the sentence "Approximately 10 mL of blood will be required for the D-dimer test" with the sentence "Approximately 3 mL of blood will be required for each D-dimer test (Baseline, Week 4 [if applicable])"
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, spelling or formatting changes were made.

Amendment INT-2 (05 December 2014)

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

The overall reason for the amendment: In many countries, chronic disease exacerbation is now managed in an outpatient setting. Recent data indicate that exacerbation of chronic heart failure is being increasingly managed with outpatient therapy. The risk of subsequent events (death, myocardial infarction, and stroke) remains high and is comparable whether patients are treated in a hospital or in an acute outpatient setting where they receive parenteral medications. With input from investigators and heart failure experts, the inclusion criteria have been modified to include high-risk patients treated in an outpatient setting with parenteral medications for decompensated heart failure.

Applicable Section(s)	Description of Change(s)
Rationale: To include high-risk patients treated in an outpatient setting with parenteral medications for decompensated heart failure.	
Synopsis (Overview of study design, Subject population); 3.1 Overview of Study Design; 4.1. Inclusion Criteria (Criterion 3.2)	The study population was modified to indicate "Eligible subjects must have an episode of decompensated heart failure (index event) requiring (a) an overnight stay in a hospital, emergency department, or medical observation facility with the capability of treating with intravenous medications and observing heart failure patients, or (b) an unscheduled outpatient visit to a heart failure management center, where parenteral therapy is required for heart failure stabilization."
Rationale: To add the term and definition for "index event" as an episode of decompensated heart failure and to keep the consistency throughout the protocol.	
Synopsis (Description of the compound); 1.2. Overall Rationale for the Study	Defined the "index event" by adding the phrase "an episode of decompensated HF, defined as the index event".
Synopsis (Description of the compound); 1.1. Background	Replaced the phrase "index hospitalization" with "inpatient or outpatient treatment"
4.1. Inclusion Criteria (Criterion 3.2)	Replaced the phrase "Exacerbation of chronic HF" with "an episode of decompensated HF".
Throughout the protocol	Replaced the phrase "hospitalization for exacerbation of HF", or "index hospitalization" with the "index event" when appropriate.
Rationale: Based on investigators' feedback regarding their standard care for follow-up visits after discharge from the index event, the randomization period was extended to "up to 30 days after discharge from the facility treating the index event".	

Applicable Section(s)	Description of Change(s)
Synopsis (Overview of study design, Subject population); T&E Schedule, (footnote "m"); 3.1 Overview of Study Design (including Figure 1, Schematic overview of the study design); 4.1. Inclusion Criteria (Criterion 3.2); 9.1.2. Screening Phase	Changed the randomization period from "up to 14 days after discharge from their index hospitalization" to "up to 30 days after discharge from the facility treating the index event".
Synopsis (Overview of study design); T&E Schedule (Table, footnote "b"); 3.1 Overview of Study Design; 4. Subject Population; 9.1.2. Screening Phase	Changed the screening period from "will last up to 35 days (up to 21 days during the index hospitalization and up to 14 days after discharge from the index hospitalization)" to "may last up to 51 days before randomization (21 days maximum for a hospitalization admission plus up to 30 days after discharge from the facility treating the index event)".
T&E Schedule (footnote "d"); 4.2. Exclusion Criteria (NOTE)	Changed the hospital/local laboratory results and imaging studies information collection period from "within 21 days of discharge" to "within 51 days (21 days maximum for a hospitalization admission plus up to 30 days after discharge from the facility treating the index event)."
4.1. Inclusion Criteria (Criterion 6.1)	Changed the phrase "2 weeks" into "30 days" for the stay period in a nursing home, rehabilitation center or other skilled facility if transferred to these places after discharge.
Rationale: To provide more clarity for BNP or NT-proBNP test	
1.2. Overall Rationale for the Study	Added the rationale for including a minimum level of BNP or NT-proBNP as requirement for entry into the study.
Synopsis (Overview of study design, Subject population); 3.1 Overview of Study Design; 4.1. Inclusion Criteria (Criterion 16)	Added the phrases "(preferred assay)" and "during the screening period and before randomization" at the end of the sentence "Subjects must also have a BNP level ≥ 200 pg/mL or NT-proBNP level ≥800 pg/mL (preferred assay) during the screening period and before randomization".
Rationale: To be consistent with languages across rivaroxaban clinical program	
4.1. Inclusion Criteria (Criterion 12)	Removed the Criterion 12 "A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction."
4.1. Inclusion Criteria (Criterion 13)	Deleted the phrase "during the study and for 3 months after receiving".
Rationale: To provide more clarity	
T&E Schedule	Switched the Column's titles "Double-Blind Treatment Phase" and "Treatment Period"
T&E Schedule (footnote "u")	Replaced the word "local" with "hematology".

Applicable Section(s)	Description of Change(s)
1.2. Overall Rationale for the Study; 3.1. Overview of Study Design	Added the phrase "(Day 1) prior to the first dose of study drug" to clarify the time for collecting blood sample for D-dimer data.
2.1. Objectives (Secondary objectives)	Added the phrase "in reducing the risk of the following outcomes:"
4.1. Inclusion Criteria (Criterion 2.1)	Deleted the phrase "documented" and "chronic" in "Subject must have ~~documented~~ symptomatic ~~chronic~~ HF for at least 3 months prior to screening", since symptoms of HF can be self-reported.
4.3. Prohibitions and Restrictions (Criterion 2.1)	Added the word "ASA"
4.3. Prohibitions and Restrictions (Criterion 5.1); 8. Prestudy and Concomitant Therapy (Prohibited therapies)	Added the phrase "within 4 days before randomization, or during the study" for strong inhibitors of cytochrome P450 3A4.
4.3. Prohibitions and Restrictions (Criterion 9)	Added a criterion required by the current protocol template that states "A man who has not had a vasectomy and is sexually active with a woman of childbearing potential must use a double-barrier method of birth control (see Section 4.1, Inclusion Criteria). All men must also not donate sperm until last dose of study drug."
8. Prestudy and Concomitant Therapy	Added "antiplatelet agents, anticoagulants, and ASA use" into the list to be recorded on the appropriate page of the eCRF.
8. Prestudy and Concomitant Therapy (Required/Allowed therapies)	Changed the subsection title from "Allowed Therapies" to "Required/Allowed Therapies".
3.1. Overveiw of Study Design; 8. Prestudy and Concomitant Therapy (Required/Allowed therapies);	Added the phrase "on a routine or as needed basis" to define diuretic use.
9.2.1. Efficacy Evaluations (Re-Hospitalization for Worsening of Heart Failure)	Added the following content "The investigator will use his/her clinical judgment to determine if the primary diagnosis for a re-hospitalization supports worsening HF or if the admission is caused by a different cardiovascular event occurring concurrently (e.g., cardiac arrhythmia). If the primary reason for the re-hospitalization could be either event, the default should be re-hospitalization for worsening HF."
9.2.1. Efficacy Evaluations (Re-Hospitalization for a CV Event)	Added the following content "MI, Stroke, DVT, PE, and spontaneous bleeding events are considered cardiovascular events. If any of these are the primary reason for a hospitalization, complete both a re-hospitalization for CV event form and the outcome event eCRF form."
9.5.1. Safety Evaluations (Bleeding outcome evaluation)	Added the phrase "or permanent study drug discontinuation" onto the list of events to be collected and entered on the eCRF bleeding event page. Clarified the phrase for a greater than 24 hour hospitalization due to non-traumatic bleeding

Applicable Section(s)	Description of Change(s)
9.5.1. Safety Evaluations (Clinical Laboratory Tests)	Added the BNP or NT-proBNP values and CK-MB and troponin values, if available, onto the list of test results with reference ranges to be obtained from the hospital lab/local lab at the time of the index event
10.2. Discontinuation of Study Treatment	Added the sentence "If study drug is permanently discontinued prior to GTED and the investigator or subject would like to resume study drug, this is permissible and the investigator's site manager should be contacted for instructions."
10.2.2. Permanent Discontinuation of Study Treatment	Removed the following content "The investigator will record any adverse events that occurred within the 30 days before the discontinuation of study medication and add a narrative for any of those adverse events that were serious. The appropriate adverse event or serious adverse event sections of the CRF are to be completed."
12.3.1. All Adverse Events	Deleted the phrase "hospitalization for" in the front of "CV signs or symptoms expected or anticipated in this population such as cardiac arrhythmia, chest pain, dyspnea, edema, ACS, and TIAs".
12.3.3. Pregnancy	Added the following content "Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required."
Reference	Added 3 publications onto the reference list.
Throughout the protocol	Changed the phrase "chronic heart failure" to "heart failure" when appropriate. Removed the wording "legally accepted representative", since this study would not have cases where "legally accepted representative" would be used
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, spelling or formatting changes were made.

Amendment INT-1 (2 May 2014)

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

The overall reason for the amendment: The overall reasons for the amendment are: 1) to extend the acceptable time window of the documented left ventricular ejection fraction (LVEF) from within 3 months before randomization to within 1 year before randomization (Inclusion Criterion 4), this change is based on imaging being done on a 3 to 12 months basis in routine clinical practice; 2) to require serum brain natriuretic peptide (BNP) or N-terminal-proBNP (NT-proBNP) level as an inclusion criterion for enrollment in the study, this change is to exclude low risk patients who may not have exacerbation of heart failure; 3) to add a new safety measure of collecting hemoglobin level at Week 12, at the request of the Independent Data Monitoring Committee (IDMC) and the Steering Committee; 4) to change the definition of hospitalization for heart failure (HF) from a minimum of 24-hour hospital stay to an overnight stay in a hospital, emergency department, or medical facility with the capability of treating with intravenous medications and observing patients with HF; 5) to provide clarification on inclusion and exclusion criteria.

Applicable Section(s)	Description of Change(s)
Rationale: Extended the acceptable time window of the documented LVEF based on imaging being done on a 3 to 12 months basis in routine clinical practice.	
Time and Events Schedule; 4.1. Inclusion Criteria	The acceptable time window of the documented LVEF has been changed from within 3 months before randomization to within 1 year before randomization.
4.2. Exclusion Criteria, Note	Same change as above.
Rationale: Added serum BNP or NT-proBNP level as an inclusion criterion for enrollment in the study, this change is to exclude low risk patients who may not have exacerbation of heart failure	
Time and Events Schedule	A new row has been added to the Time and Event Schedule to collect BNP or NT-proBNP level at screening.
Synopsis, Subject Population	Requirement for a minimum level of BNP or NT-proBNP level at screening for study entry is added.
3.1 Overview of Study Design	Added "Subjects must also have a brain natriuretic peptide (BNP) level ≥200 pg/mL or N-terminal-proBNP (NT-proBNP) level ≥800 pg/mL"
4.1. Inclusion Criteria	A new inclusion criterion has been added to require a minimum BNP or NT-proBNP level at screening for study entry.
9.1.1. (Study Procedures) Overview	The following text has been added: "Blood for BNP or NT proBNP measurements will be drawn prior to randomization as part of the inclusion criteria. If available, BNP or NT-proBNP will be measured by the local hospital laboratory. If local measurements of BNP or NT-proBNP are not available, approximately 5 mL of blood will be sent to a local central laboratory for measurement of BNP or NT-proBNP (whichever is available at that laboratory)."
Rationale: Added a new safety measure of collecting hemoglobin level at the request of the IDMC and the Steering Committee.	
Time and Events Schedule; 9.1.1. (Study Procedures) Overview	A new safety measure of collecting hemoglobin level at a local lab at Week 12 (no later than Week 24) has been added. Approximately 3-5 mL of blood will be required for the hemoglobin test.

Applicable Section(s)	Description of Change(s)
Rationale: Added the recording of creatine kinase muscle and brain subunit (CK-MB), troponin levels.	
Time and Events Schedule	A new row and a footnote have been added to the Time and Event Schedule to capture the recording of CK-MB and troponin levels if available during the index hospitalization.
9.1.1. (Study Procedures) Overview	The following text has been added: If available during the index hospitalization, the value of CK-MB, troponin levels should be recorded in the local lab section of the eCRF.
Rationale: Clarified when unscheduled visits should be done.	
Time and Events Schedule	Footnotes have been added to the Time and Events Table to clarify when unscheduled visits should occur.
9.1.3. Double-Blind Treatment Phase	For outcome events and after a discharge for any re-hospitalization, the following text has been deleted: "~~where the next scheduled visit is 2 or more months later~~"
Rationale: Clarified when replacement for lost medication should be dispensed.	
Time and Events Schedule	Footnotes have been added to the Time and Events Table to clarify that lost medication requiring replacement should be dispensed at an unscheduled visit before the next scheduled visits.
Rationale: Defined the index hospitalization and re-hospitalization for HF. Due to a trend in treating patients with HF with shorter hospital stays, as well as treating them in out-patient settings, a minimum of overnight stay will be required to consider the admission as the index hospitalization.	
Synopsis, Overview of Study Design; Synopsis, Subject Population; 4.1. Inclusion Criteria; 9.2.1. Efficacy Evaluations	The index hospitalization (and re-hospitalization for HF) has been defined as an overnight stay (ie, staying past midnight) in a hospital, emergency department, or medical facility with the capability of treating with intravenous medications and observing patients with HF.
Rationale: Extended screening period after index hospital discharge.	
Synopsis, Overview of Study Design; Synopsis, Subject Population; Time and Events Schedule; Section 3.1. Overview of Study Design; Section 4. Subject Population; 9.1.2. Screening Phase	Subjects have up to 14 days (changed from 7 days) after discharge to enroll, as a result the screening period is extended to 35 days (from 28 days).
Rationale: Clarified the dose of aspirin.	
Synopsis, Overview of Study Design; 3.1. Overview of Study Design; 8. Prestudy and Concomitant Therapy	The dose of aspirin should be 100 mg or less per day, unless not clinically appropriate.
Rationale: Clarified how missed doses should be taken and documented.	

Applicable Section(s)	Description of Change(s)
Synopsis, Dosage and Administration; 6. Dosage and Administration;	A missed dose should be taken as soon as possible, up to 6 hours after the scheduled dosing time. If >6 hours has elapsed after the scheduled time the dose should be skipped and the next dose should be taken at the regular time. Unintentional stopping of study drug for more than 7 consecutive days should be documented.
Rationale: Clarified subjects discharged from the index hospitalization to a nursing home must have a stay of 2 weeks or less so that subject will be in a home environment at time of randomization.	
4.1. Inclusion Criteria	Inclusion Criterion number 6 has been updated to state that if the subject is transferred to a nursing home, rehabilitation center or other skilled facility, the stay must be 2 weeks or less so that the subject will be in a home environment at the time of randomization.
Rationale: Clarified criteria for diuretic, angiotensin receptor blocker (ARB), beta-blocker and aldosterone antagonist therapy	
4.1. Inclusion Criteria	Inclusion Criterion number 7 has been updated to clarify the criteria for diuretic, ARB, beta-blocker and aldosterone antagonist therapy.
Rationale: Clarified criteria for safety purposes	
4.1. Inclusion Criteria	Added additional instructions for subjects who had been receiving prophylactic anticoagulation prior to randomization.
Rationale: Clarified the window of cardiac surgeries and procedures.	
4.2. Exclusion Criteria	Clarification that planned cardiac surgery within 28 days either prior to *or after* randomization, excluding PCIs and devices, and implantation of an electrophysiologic device such as implantable cardioverter defibrillator or pacemaker planned to occur within *14 days* either prior to *or after* randomization will exclude subjects from entering the study.
Rationale: Clarified the definitions of "ventricular tachycardia", "significant liver disease", "severe peptic ulcer disease" and "severe thrombocytopenia".	
4.2. Exclusion Criteria	Definitions of "ventricular tachycardia", "significant liver disease", "severe peptic ulcer disease" and "severe thrombocytopenia" are provided.
Rationale: Removed ticagrelor and prasugrel from prohibited medication as the use of these antiplatelet medications is increasing in patients undergoing PCI and stent placement. The use of these newer agents will be according to labeling.	
4.1. Inclusion Criteria; 4.3. Prohibitions and Restrictions;	Ticagrelor is no longer a prohibited antiplatelet medication. Prasugrel is prohibited only in subjects who are ≥75 years old in age, or in subjects with prior TIA or stroke.
8. Prestudy and Concomitant Therapy	The following text has been added to **Allowed Therapies**: Clopidogrel, ticlopidine, and ticagrelor may be used if indicated. Prasugrel may also be used if indicated, but not in subjects with a prior history of TIA or stroke or those who are 75 years of age or older. There is limited data on the combined use of rivaroxaban with either ticagrelor or prasugrel. The IDMC will monitor any increased risk to the subjects in this study using these combinations. The use of clopidogrel, ticlopidine, ticagrelor, or prasugrel should be prescribed according to the approved labeling for each drug.
Rationale: Clarified the documentation of prestudy and concomitant therapy.	

Applicable Section(s)	Description of Change(s)
8. Prestudy and Concomitant Therapy	The following text has been added (in italic) or modified (strikethrough): *Relevant concomitant medications or treatment (eg, antibiotics for sepsis or surgical interventions) given for adverse events and* ~~chronic~~ use of other prohibited therapies, as specified below, will be documented on the appropriate page of the eCRF as well.
Rationale: Clarified the timing of D-dimer collection.	
9.3. Biomarkers	Blood will be collected for D-dimer measurement prior to the first dose of study drug, instead of prior to randomization.
Rationale: Clarified the reporting of bleeding outcomes.	
9.5.1. Safety Evaluations, Bleeding Outcome Evaluations	To clarify that bleeding events are not reported as adverse events; To clarify that non-traumatic bleeding events are considered CV in origin. A Re-hospitalization for CV Event eCRF page is required for subjects who are hospitalized for greater than 24 hours for bleeding. In addition, a discharge summary indicating the primary reason for admission as bleeding is required; To add the text in italics: "For subjects hospitalized for a bleeding event, the admission hemoglobin *and the lowest hemoglobin*, or hematocrit (if hemoglobin is not available) will be entered on the eCRF as well as the final hemoglobin or hematocrit (closest to discharge)."
Rationale: Clarified that hemoglobin, not hematocrit, is to be collected.	
9.5.1. Safety Evaluations, Clinical Laboratory Tests	Hematocrit has been removed from the hematology panel.
Rationale: Removed pooling of efficacy data by country.	
11.3. Efficacy Analyses, Primary Endpoint	The following test has been deleted: ~~If necessary, countries with few events will be pooled. Pooling algorithm will be defined in the SAP.~~
Rationale: Defined the minimum length of time spent in the hospital for serious adverse events.	
12.1.1. Adverse Event Definitions and Classifications; 12.3.2. Serious Adverse Event	The minimum length of hospitalization for serious adverse events has been defined as 24 hours (including time spent both in the emergency department and the in-patient room).
Rationale: Clarified the criteria for collecting adverse events and serious adverse events.	
12.3.1. All Adverse Events	Clarification of how bleeding events will be captured.
Rationale: Clarified the recording of outcome events and adverse events between ICF signing and randomization.	
12.3.1. All Adverse Events	The following text has been added: If any outcome event or adverse event occurs from the time a signed ICF is obtained until randomization, this event will be recorded as an adverse event or an SAE on the eCRF.
Rationale: The FDA indicated that the protocol would not qualify for an exception from informed consent requirements for emergency research.	
16.2.3. Informed Consent	The last paragraph of the section regarding emergency consent exception has been deleted.

Applicable Section(s)	Description of Change(s)
Rationale: Clarified the enoxaparin dose adjustment calculation.	
Attachment 3; Attachment 4	If additional enoxaparin is needed, the dose would be the desired dose minus the dose provided in the table at the specific time point.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

STUDY TITLE

A Randomized, Double-blind, Event-driven, Multicenter Study Comparing the Efficacy and Safety of Rivaroxaban with Placebo for Reducing the Risk of Death, Myocardial Infarction or Stroke in Subjects with Heart Failure and Significant Coronary Artery Disease Following an Episode of Decompensated Heart Failure

DESCRIPTION OF THE COMPOUND

Rivaroxaban is an oral, direct acting, Factor Xa (FXa) inhibitor anticoagulant which has been developed for the treatment of several thrombosis-mediated conditions. The clinical development program for rivaroxaban is extensive, with over 70,000 subjects having been studied from Phase 1 through large Phase 3 studies covering several indications and potential indications. Approximately 40,000 of these subjects have received rivaroxaban. Rivaroxaban is marketed under the trade name XARELTO® and has been approved for multiple indications worldwide.

Heart Failure (HF) is a prothrombotic disease and thrombosis may be associated with increased morbidity and mortality. For the last 15 to 20 years, more research has centered around the hypercoagulable state that occurs in HF patients. It has been observed in clinical studies that subjects with HF have higher circulating levels of pro-coagulants. In addition, autopsy studies of subjects with HF who died suddenly during a clinical trial had a high rate of myocardial infarction (MI) or acute coronary events. Studies and guidelines have reported that the prognosis after inpatient or outpatient treatment of an episode of decompensated HF is poor with a 50% readmission rate at 6 months and a 25% to 35% mortality rate at 12 months.

Although the results of previous studies with warfarin have demonstrated that anticoagulation is associated with reduced rates of important clinical events in patients with HF, results of these studies have not been conclusive. In a recent Phase 3 study of rivaroxaban in acute coronary syndrome (ACS), rivaroxaban was shown to reduce the incidence of the primary endpoint (cardiovascular [CV] death, MI, or stroke) in a subset of subjects with a history of HF (see Table 1 of the protocol). This supports the hypothesis that rivaroxaban may help reduce thrombotic events in patients with HF that can lead to death, MI or stroke. Thus, a large prospectively designed study with a novel anticoagulant is warranted to adequately address whether or not rivaroxaban can reduce the risk of death, MI, and stroke in patients with HF and significant coronary artery disease (CAD), following an episode of decompensated HF, defined as the “index event”.

This study is designed to be a pivotal Phase 3 study, with adequate power to determine if the use of the Factor Xa inhibitor rivaroxaban in addition to standard HF therapy can reduce the risk of important clinical outcome events (ie, all-cause mortality [ACM], MI, and stroke) in patients with HF and significant CAD. The addition of another therapeutic approach to reduce the risk of morbidity and mortality in HF patients would fulfill a substantial unmet medical need.

OBJECTIVES AND HYPOTHESES

Primary Objective

- The primary objective is to demonstrate that rivaroxaban is superior to placebo in subjects with HF and significant CAD, who are receiving standard care, in reducing the risk of the composite of ACM, MI, or stroke following an index event.

Secondary Objectives

The secondary objectives are to compare rivaroxaban with placebo in addition to standard care in subjects with HF and significant CAD following an index event in reducing the risk of the following outcomes:

- Composite of CV mortality or re-hospitalization for worsening of HF
- CV mortality
- Re-hospitalization for worsening of HF
- Re-hospitalization for CV events

Exploratory Objectives

The exploratory objectives are to compare rivaroxaban with placebo in addition to standard care in subjects with HF and significant CAD following an index event.

- Selected medical resource utilization (MRU) data on re-hospitalization for CV events and for worsening of HF
- Symptomatic deep vein thrombosis (DVT)
- Symptomatic pulmonary embolism (PE)
- Benefit-risk balance

Safety Objectives

The safety objectives are to compare the occurrence of the following bleeding events with rivaroxaban and placebo in addition to standard care in subjects with HF and significant CAD following an index event:

- The composite of fatal bleeding or bleeding into a critical space (intracranial, intraspinal, intraocular [vitreous or retinal], pericardial, intra-articular, retroperitoneal, intramuscular with compartment syndrome) with a potential for permanent disability
- Bleeding events requiring hospitalization
- Major bleeding events using the International Society on Thrombosis and Haemostasis (ISTH) bleeding criteria

Overall safety will also be assessed.

Hypothesis

The primary hypothesis of this study is that rivaroxaban 2.5 mg taken orally twice a day (in addition to standard care) is superior to placebo (in addition to standard care), in subjects with HF and significant CAD following an index event in reducing the risk of the composite of ACM, MI, or stroke.

OVERVIEW OF STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter, event-driven, superiority study of rivaroxaban with clinical outcome assessments in subjects with symptomatic HF (3 months or longer) and significant CAD. The subject population comprises men and women age 18 and over who have a diagnosis of previous MI or significant CAD with a left ventricular (LV) dysfunction (left ventricular ejection fraction [LVEF]) ≤40%). Only subjects treated for decompensated HF will be eligible for enrollment.

Eligible subjects must have an episode of decompensated HF (index event) requiring (a) an overnight stay in a hospital, emergency department, or medical observation facility with the capability of treating with intravenous medications and observing HF patients, or (b) an unscheduled outpatient visit to a HF management center, where parenteral therapy is required for HF stabilization. Subjects must also have a brain natriuretic peptide (BNP) level ≥ 200 pg/mL or N-terminal-proBNP (NT-proBNP) level ≥800

pg/mL (preferred assay) during the screening period and before randomization. Subjects have up to 30 days after discharge to be randomized if they are in stable condition.

The primary efficacy outcome is the composite of ACM, MI, or stroke. The principal safety outcome is the composite of fatal bleeding or bleeding into a critical space (intracranial, intraspinal, intraocular, pericardial, intra-articular, retroperitoneal, intramuscular with compartment syndrome) with a potential for permanent disability. Additional bleeding outcomes are bleeding events requiring hospitalization, and ISTH major bleeding events.

A total of 1,200 primary efficacy outcome events are targeted to demonstrate the superiority of rivaroxaban compared with placebo. A sample size of approximately 5,000 subjects will be randomized. Subjects who meet all of the inclusion and none of the exclusion criteria will be randomly assigned to receive either rivaroxaban or placebo. Randomization will be stratified by country. After randomization, subjects will receive double-blind treatment (oral rivaroxaban 2.5 mg or matching placebo b.i.d.). All subjects will also receive standard care based on international clinical guidelines for HF and CAD as prescribed by their managing physicians. Standard care is expected to include a diuretic, renin angiotensin system (RAS) inhibitor/vasodilator therapy (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers or hydralazine/nitrates), beta blocker therapy, aldosterone antagonist if indicated, and aspirin/acetylsalicylic acid (ASA) (or other antiplatelet agent as appropriate). The dose of ASA should be 100 mg or less per day, unless not clinically appropriate. Dual antiplatelet therapy is allowed where indicated.

The study consists of a screening phase, a double-blind treatment phase, and a follow-up after the sponsor-announced global treatment end date (GTED, defined as the date when 1,200 primary efficacy outcome events are predicted to have occurred) which is also the End of Study (EOS) visit. The screening phase may last up to 51 days before randomization (21 days maximum for a hospitalization admission plus up to 30 days after discharge from the facility treating the index event), followed by an estimated 6 to 54 months double-blind treatment phase. The average duration of participation for a subject in the study is expected to be approximately 29 months.

Subjects are expected to remain in the double-blind treatment phase until the GTED. The date is based on site local time. The study sites will be notified of the GTED at which time subjects will be instructed to discontinue study drug (after taking both their AM and PM doses on GTED) and return to the study site for the EOS visit (30±15 days, but no sooner than 15 days after the GTED). Efficacy and safety outcome events will be collected at the EOS visit.

Subjects who permanently discontinue the study drug before the GTED will complete the Early Permanent Study Drug Discontinuation visit as soon as possible after the last dose of study drug. In addition, these subjects should return for all scheduled visits, including the EOS visit. If these subjects refuse office visits, the investigator is asked to strongly encourage the subjects to allow regular contact (eg, by telephone) until study end, according to the TIME AND EVENTS SCHEDULE, either with them, or with a close friend, relative, or their primary care physician to determine vital status and if an efficacy or safety outcome event has occurred.

A subject will be considered as having completed the double-blind treatment phase, if the subject continues taking double-blind study drug until either the announced GTED or within 7 days before the death of the subject. If a subject experiences an outcome event such as MI or stroke, study drug may be temporarily held if necessary or if using other anticoagulant drugs or thrombolytic therapy. This also applies to other efficacy outcome events such as DVT or PE. After the appropriate treatment of the outcome event, the investigator may choose to resume study medication for the subject. However, study medication must be permanently discontinued for any intracranial hemorrhage or for any reason listed in Section 10.2.2.

Vital status will be collected for all subjects who permanently discontinue study drug early, withdraw from the study, or are lost to follow-up, either by telephone or in person at the EOS visit, or if applicable, by a review of subject's medical or public records unless this contact is not allowed by local regulations.

A Steering Committee and an Independent Data Monitoring Committee (IDMC) will be commissioned for this study. The IDMC will review unblinded safety data periodically to ensure the safety of study subjects. If necessary or requested by the IDMC, subject level unblinded data may be provided to the IDMC (see Section 11.8 of the protocol for more details). In addition, the IDMC will review results of the planned interim analysis and make a recommendation whether the study should be terminated prematurely due to overwhelming benefit or futility (see Section 11.9 of the protocol for more details). No independent Clinical Event Committee will be used for adjudication of outcome events in this study.

SUBJECT POPULATION

The subject population comprises men and women age 18 years and older with HF (3 months or longer) and significant CAD with LV dysfunction (LVEF ≤40%). Significant CAD is defined as: documented previous MI, history of prior coronary artery bypass graft, coronary angiography demonstrating at least 50% stenosis of one or more arteries, history of percutaneous coronary intervention (PCI) with or without stent, or for those with no documented history of MI, electrocardiogram (ECG) evidence (Q waves) with corresponding wall motion abnormality on echocardiogram at any point during the index event period to randomization. Eligible subjects must have an episode of decompensated HF (index event) requiring (a) an overnight stay in a hospital, emergency department, or medical observation facility with the capability of treating with intravenous medications and observing HF patients, or (b) an unscheduled outpatient visit to a HF management center, where parenteral therapy is required for HF stabilization. Subjects must also have a BNP level ≥ 200 pg/mL or NT-proBNP level ≥800 pg/mL (preferred assay) during the screening period and before randomization. Subjects have up to 30 days after discharge to be randomized if they are in stable condition.

DOSAGE AND ADMINISTRATION

Subjects will be randomly assigned in a 1:1 ratio to receive oral rivaroxaban 2.5 mg or placebo b.i.d. (each in addition to standard of care for HF and CAD as prescribed by their managing physician). Randomization will be stratified by country.

All subjects will receive study drug (rivaroxaban or placebo) orally twice daily; once in the morning and once in the evening, with or without food, at approximately the same times each day throughout the study. Once the GTED is reached, all subjects who are receiving study drug should discontinue study drug (after taking both their AM and PM doses on GTED) and complete the EOS visit (refer to TIME AND EVENTS SCHEDULE).

A missed dose should be taken as soon as possible (up to 6 hours after the scheduled dosing time), and the next scheduled dose should be taken at the regular time. If >6 hours has elapsed after the scheduled time the dose should be skipped and the next dose should be taken at the regular time. An occasional forgotten dose need not be recorded. Intentional stopping of study drug by the subject, unintentional stopping of study drug for more than 7 consecutive days, or direction to temporarily stop study drug by the investigator or other physician will be documented and recorded in the eCRF.

Throughout the study, study drug will be dispensed at appropriate intervals (see the TIME AND EVENTS SCHEDULE) to ensure that subjects have adequate quantities of study drug between study visits.

Interruption of Study Drug

Study drug may be interrupted temporarily as necessary for invasive procedures or as medically needed (eg, in the setting of a bleeding event or a required prohibited therapy). Regardless of the duration

of interruption, subjects may be restarted on study drug, except for those subjects who had an intracranial hemorrhage. These will be recorded on the electronic Case Report Form (eCRF).

EFFICACY EVALUATIONS/OUTCOMES

This is a clinical outcome study. The primary efficacy outcome is the composite of ACM, MI, or stroke.

Secondary efficacy outcomes are:

- Composite of CV mortality or re-hospitalization for worsening of HF
- CV mortality
- Re-hospitalization for worsening of HF
- Re-hospitalization for CV events

Exploratory outcomes are:

- Selected MRU data on re-hospitalizations for CV events and for worsening of HF
- Symptomatic DVT
- Symptomatic PE

SAFETY EVALUATIONS/OUTCOMES

- The principal safety outcome is the composite of fatal bleeding or bleeding into a critical space (intracranial, intraspinal, intraocular [vitreous or retinal], pericardial, retroperitoneal, intra-articular, intramuscular with compartment syndrome) with a potential for permanent disability.
- Additional bleeding outcomes are bleeding events requiring hospitalization, and ISTH major bleeding events.

STATISTICAL METHODS

Sample Size Justification

This is an event driven study. The study was initially designed to observe occurrences of the primary efficacy event in 984 unique randomized subjects, on or before the GTED, to have 90% power to detect a 20% relative risk reduction (RRR, defined as subtracting the hazard ratio [test to control] from 1) in the composite of ACM, MI, or stroke at a 5%, 2-sided statistical significance level. A total of approximately 5000 subjects will be randomized to either the rivaroxaban group or the placebo group in a 1:1 ratio. If the event rate is lower than expected, the sample size may be increased by up to 500 subjects.

The above sample size calculation was estimated based on the following assumptions:

- Effect size: 20% RRR
- Event rate in the placebo arm: 19%/year
- Power: 90%
- Over all α level: 5%, 2-sided
- Permanent premature treatment discontinuation rate: 10%/year
- Lost-to-follow-up: 1%/year
- Duration of enrollment period: 24 months, based on a non-uniform enrollment distribution
- Duration of study (from First-Patient-Randomization to GTED): 31 months

The assumptions of RRR and event rate were based on observations from congestive HF subjects (the HF subgroup) in the ATLAS ACS 2 TIMI 51 study and review of literature (see Section 11.2 of the protocol for more details).

The study is revised to observe occurrences of the primary efficacy event in 1,200 unique randomized subjects based on a blinded simulation study performed on currently available trial data (ie, longer enrollment period, lower than anticipated primary efficacy event rate, higher than anticipated study drug discontinuation rate). Further details are described in the Statistical Analysis Plan (SAP).

Analyses – Efficacy

The primary efficacy analysis endpoint is the time from randomization to the first occurrence of death, MI, or stroke. The associated statistical null hypothesis is that there is no difference between treatment groups in distribution of the time, and the alternative hypothesis is that there is a difference between treatment groups.

The primary statistical hypothesis will be tested using a log-rank test, stratified by region. In addition to the final analysis, an interim analysis is planned. The primary analysis will include all events up to and including the GTED based on site local time/date (up to the cut-off date in the interim analysis), in all randomized subjects with valid informed consent signed. Subjects will be analyzed according to the treatment group to which they are randomized, regardless of actual treatment received. The overall α level is 5%, 2-sided. A Lan-DeMets α spending function with O'Brien-Fleming type of boundaries will be used to preserve the overall type I error rate.

The cumulative event rate derived from Kaplan-Meier estimate will be displayed graphically to evaluate the timing of event occurrence and the consistency of the treatment effect over time. The RRR will be estimated using a Cox proportional hazards model, stratified by region, with treatment (as randomized) as the only covariate.

Homogeneity of treatment effects, both in RRR and direction will be evaluated for the following subgroups.

- Age (< 65 vs ≥ 65; < 75 vs ≥ 75 years)
- Sex (men vs women)
- LVEF (≤30% vs > 30%; ≤ median vs > median)
- Estimated glomerular filtration rate (Modification of Diet in Renal Disease formula value <30, 30 to <60, 60 to <90, ≥90 mL/min/1.73 m^2)
- Baseline D-dimer level by quartile
- BNP, NT-proBNP (≤ median vs > median)
- History of diabetes (yes vs no)
- History of stroke (yes vs no)
- History of MI (yes vs no)
- Hypertension (yes vs no)
- Body Mass Index (<25, 25 to <30, ≥30 kg/m^2)
- Baseline digoxin use (yes vs no)
- Baseline β-blocker use (yes vs no)
- Baseline aldosterone inhibitors (yes vs no)

- Baseline angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) (yes vs no)
- Baseline aspirin use (yes vs no)
- Baseline aspirin vs dual antiplatelet use
- Baseline thienopyridine use (yes vs no)
- NYHA (Class II, III, IV)
- Race (White vs others)
- Race (White, Asian, other)
- Region

If superiority of rivaroxaban over placebo in reducing the risk of the primary efficacy endpoint is established, treatment effects in secondary endpoints will be tested subsequently in the hierarchical order:

1) Composite of CV mortality or re-hospitalization for worsening of HF
2) CV mortality
3) Re-hospitalization for worsening of HF
4) Re-hospitalization for CV events

Statistical significance is required before testing the next hypothesis in the hierarchical test procedure. These secondary endpoints will be analyzed using time-to-event analysis methods described above for the primary endpoint.

Analyses - Safety

Safety analysis will include randomized subjects who receive at least 1 dose or partial dose of study drug.

The analysis methods used for the primary efficacy endpoint will be used for the following safety endpoints. However, there are no stopping boundaries defined for these safety endpoints. Instead, nominal p-values will be reported.

- Principal safety endpoint, which is the composite of fatal bleeding or bleeding into a critical space with potential for permanent disability
- Bleeding requiring hospitalization
- ISTH major bleeding event

In addition, summary statistics will be provided for all other reported bleeding events.

Verbatim terms reported in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). For each MedDRA preferred term, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. Additional summaries, listings, or subject narratives may be provided, as appropriate.

EUDRACT number: 2013-000046-19

TIME AND EVENTS SCHEDULE

Period/Phase	Screening Period[a,b,c,d]	Double-Blind Treatment Phase					Follow-Up After GTED
		Baseline[a]	Treatment Period				
Day/Week	Day -51 to Day -1	Day 1/ Randomization	Week 4 (Day 28)	Week 12 (Day 84)	q12wk[e,f] (q84d)	Early Permanent Study Drug Discontinuation	End of Study[g]
Window / Study Procedure	21 days maximum for a hospitalization admission plus up to 30 days after discharge		-4/+2 days	-/+4 days	-/+6 days		30±15 days
Screening/Administrative							
Informed consent (ICF)	X	X[h]					
Inclusion/exclusion criteria	X	X[i]					
Review medical history requirements (including history of smoking)	X						
Demographics, body weight, height, pulse and blood pressure	X						
Preplanned surgical/procedure(s)	X	X[i]					
Urine or serum pregnancy test[j]		X[i]				X[k]	X[k]
BNP or NT-proBNP[l]	X						
Study Drug Administration							
Randomization		X[m]					
Record NYHA classification		X				X	X
Record LVEF		X[n]					
Dispense study drug[o]		X		X	X		
First dose of study drug administered in clinic[p]		X					
Study drug administration[q,r]		X	X	X	X		
Study drug accountability		X	X	X	X	X	X
Safety and Efficacy Assessments							
Clinical status review: record outcome events[s]	X	X	X	X	X	X	X
Adverse events assessment[t]	X	X	X	X	X	X	X
Review concomitant medications related to subject's HF and CAD	X	X	X	X	X	X	X

Period/Phase	Screening Period[a,b,c,d]	Double-Blind Treatment Phase					Follow-Up After GTED
		Baseline[a]	Treatment Period				
Day/Week	Day -51 to Day -1	Day 1/ Randomization	Week 4 (Day 28)	Week 12 (Day 84)	q12wk[e,f] (q84d)	Early Permanent Study Drug Discontinuation	End of Study[g]
Window / Study Procedure	21 days maximum for a hospitalization admission plus up to 30 days after discharge		-4/+2 days	-/+4 days	-/+6 days		30±15 days
Review antiplatelet, anticoagulant, proton pump inhibitors, prothrombin complex concentrates, and prohibited medications	X	X	X	X	X	X	X
Medical resource utilization			X	X	X	X	X
Hemoglobin[u]	X[k,v]			X[w]			
Platelet count, automated	X[k,v]						
Serum creatinine for eGFR[x]	X[k,v]						
Modified Rankin Evaluation, if stroke outcome event occurred				X[y]	X[y]	X[y]	X[y]
Biomarkers							
D-dimer		X[z]	X[aa]				
CK-MB, troponin	X[ab]						

Key: BNP=brain natriuretic peptide; CAD=coronary artery disease; CK-MB=creatine kinase muscle and brain subunit; eGFR=estimated glomerular filtration rate; HF=heart failure; GTED=global treatment end date; LVEF= left ventricular ejection fraction; NYHA= New York Heart Association; NT-proBNP=N terminal-proBNP; q12wk=every 12 weeks.

a All screening evaluations must be completed before randomization. Both screening and baseline evaluations may occur on the day of randomization (defined as Day 1).

b The screening period may last up to 51 days before randomization (21 days maximum for a hospitalization admission plus up to 30 days after discharge from the facility treating the index event).

c Laboratory screening assessments that are part of the standard care performed by the investigator do not need to be repeated if performed within the timeframe required by the protocol.

d Hospital/local laboratory results and imaging studies (within 51 days [21 days maximum for a hospitalization admission plus up to 30 days after discharge from the facility treating the index event]) will be used for screening purposes and will serve as the baseline (Day 1) laboratory results.

e Treatment visit every 12 weeks until the global treatment end date (GTED) when pre-specified number of primary efficacy outcome events is estimated to be reached.

f At the GTED subjects will be instructed to stop their study drug and return to the study site 30 Days (±15 days) for the End-of-Study visit.
Subjects who permanently discontinue the study drug before the GTED will complete the Early Permanent Study Drug Discontinuation visit as soon as possible after their last dose of study drug. In addition, every attempt will be made to follow these subjects for all subsequent scheduled visits until EOS.

g Contact will take place 30±15 days, but no sooner than 15 days after the GTED to assess efficacy and safety outcomes. For subjects who discontinue study drug prematurely this contact will take place within the same time frame after the GTED. See Section 9.1.4.

h If subject is screened and randomized the same day.

i To be reviewed before randomization.

j To be performed on all women of childbearing potential. 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.

k Use local laboratory results for the inclusion and exclusion clinical laboratory parameters and for early permanent study drug discontinuation or the GTED visits. All screening clinical laboratory results must be completed and reviewed before randomization.

l Blood for BNP or NT proBNP measurements will be drawn prior to randomization as part of the inclusion criteria. If available, BNP or NT-proBNP will be measured by the local hospital laboratory. If local measurements of BNP or NT-proBNP are not available, approximately 5 mL of blood will be sent to a local central laboratory for measurement of BNP or NT-proBNP (whichever is available at that laboratory).

m Subjects will be randomized up to 30 days after discharge from the facility treating the index event.

n Documented within 1 year before randomization. If more than one LVEF is available the most recent one should be used.

o Study drug will be dispensed on Day 1 after randomization and every scheduled visit thereafter except Week 4 until end of treatment. Lost medication requiring replacement should be dispensed at an unscheduled visit before the next scheduled visits.

p If the first dose of study drug is taken prior to or at 12:00 PM (noon), it is considered the AM dose of the day and a PM dose should also be taken. If it is taken after 12:00 PM (noon), it is considered the PM dose of the day and another pill should not be taken that day.

q Subjects will self-administer study drug once in the morning and once in the evening (approximately 12 hours apart), at approximately the same times each day.

r Subjects who experience any outcome events (except for death and hemorrhagic stroke) may continue to receive blinded study drug and complete all scheduled visits.

s When an outcome event occurs, or after discharge for any re-hospitalization, an unscheduled visit before the next scheduled visit should be done for clinical status review and outcome event recording.

t See Section 9.5, Safety Evaluations and Outcomes for adverse events that will be recorded. Based upon the severity of the adverse event and clinical judgment of the investigator, an unscheduled visit before the next scheduled visit may be needed to assess adverse events.

u If the subject is re-hospitalized for bleeding at any time after randomization, and a hemoglobin or hematocrit test is done, the result should be recorded on the hematology lab page(s) in the eCRF.

v Test result closest to randomization should be used.

w If a hemoglobin collection is not done at the local lab at Week 12 (±14 days), it should be collected no later than Week 24 (+ 14 days).

x Creatinine concentration for eGFR will be calculated by the interactive web response system using the Modification of Diet in Renal Disease formula (Attachment 1).

y A Modified Rankin Evaluation (Attachment 2) will be obtained between 6 and 18 weeks following a stroke outcome event or at End of Study, whichever occurs first.

z To be collected from all subjects prior to the first dose of study drug and analyzed by the central laboratory.

aa To be collected from approximately 10% of randomly selected subjects within each country and analyzed by the central laboratory.

ab If available during the index event, the value of CK-MB and/or troponin should be recorded on the lab page(s) of the eCRF (if more than one test values are available, use the highest value).

ABBREVIATIONS

ACE	angiotensin-converting enzyme
ACEI	angiotensin-converting enzyme inhibitor
ACM	all-cause mortality
ACS	acute coronary syndrome
AFib	Atrial fibrillation
ARB	angiotensin receptor blockers
ASA	acetylsalicylic acid
BNP	brain natriuretic peptide
CABG	coronary artery bypass graft
CAD	coronary artery disease
CCU	Critical Care Unit
CK-MB	creatine kinase-muscle and brain subunit
CRF	case report form
CV	cardiovascular
DCF	data clarification form
DCM	dilated cardiomyopathy
DVT	deep vein thrombosis
ECG	electrocardiogram
eCRF	electronic case report form
eDC	electronic data capture
EF	ejection fraction
eGFR	estimated glomerular filtration rate
EOS	End-of-Study
ER	emergency room
FXa	Factor Xa
GCP	Good Clinical Practice
GTED	Global Treatment End Date
HF	heart failure
HR	hazard ratio
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IHD	ischemic cardiomyopathy
IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intent-to Treat
IWRS	interactive web response system
LBBB	left bundle branch block
LOS	length of stay
LV	left ventricular
LVEF	left ventricular ejection fraction
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MRU	medical resource utilization
NT-proBNP	N-terminal-pro- brain natriuretic peptide
PCC	prothrombin complex concentrates
PCI	percutaneous coronary intervention
Pcr	Plasma creatinine
PE	pulmonary embolism
PQC	Product Quality Complaint
PRO	patient-reported outcome(s)
RAS	renin angiotensin system
RRR	relative risk reduction

TIA	transient ischemic attack
ULN	upper limit of normal
US	United States
VTE	venous thromboembolism

1. INTRODUCTION

Rivaroxaban is an oral, direct acting, Factor Xa (FXa) inhibitor anticoagulant that has been developed for the treatment of several thrombosis-mediated conditions. The clinical development program for rivaroxaban is extensive, with over 70,000 subjects having been studied from Phase 1 through multiple large Phase 3 studies covering several indications and potential indications. Approximately 40,000 of these subjects have received rivaroxaban. Rivaroxaban is marketed under the trade name XARELTO® and has been approved in multiple indications worldwide.

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

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

There are approximately 5.7 million people in the United States (US) suffering from heart failure (HF), and of that number approximately 57,000 die each year as a direct result of HF[21]. In addition, it has been estimated that there are about 6.5 million HF patients in Europe. Despite many recent advances in the treatment of HF both pharmacologically (eg, angiotensin-converting enzyme [ACE] inhibitors, beta blockers) and with devices (eg, implantable defibrillators), morbidity and mortality remain high. Overall, approximately 50% of HF patients die within 4 years of diagnosis[8]. It remains the most costly disease with respect to hospitalization in the US. The estimated direct cost for HF in the US in 2009 was almost $34 billion[15].

For the last 15 to 20 years, research has centered around the hypercoagulable state that occurs in HF patients[6]. It has been observed in clinical studies that subjects with HF have higher circulating levels of procoagulants[4]. In addition, autopsy studies of HF subjects who died suddenly during a clinical trial had high rates of MI or acute coronary events[27].

Approximately 50% of HF patients have a history of a previous MI and about 70% have known significant coronary artery disease (CAD) with sudden death being a major cause of mortality[3]. In a large subgroup of subjects with HF in the ATLAS ACS 2 TIMI 51 trial, it was observed that the rivaroxaban dose groups had decreased rates of CV events and death compared with the placebo control group, which was consistent with the overall study findings (Clinical Study Report ATLAS ACS 2 TIMI 51). Subjects in both groups were taking background therapy of aspirin, and most were also taking a thienopyridine. This finding combined with the results of previous smaller studies on the hypercoagulable state that occurs in HF provides the basis for the exploration of the effect of rivaroxaban in similar patients with significant CAD but without a recent acute coronary syndrome (ACS) event.

Studies and guidelines have reported that the prognosis after an index hospitalization for HF is poor with a 50% hospital readmission rate at 6 months and a 25% to 35% mortality rate at 12 months[14]. In a review of the CHARM study, subjects were noted to be at a higher risk of death and re-hospitalization if they were hospitalized for HF exacerbation during the study[23]. This risk

was the greatest over the first 6 months and gradually returned to the risk of non-hospitalized subjects in that study after a year. The pathophysiology for this high mortality is not well understood, but there may be recurrent thrombotic events that occur as the subjects transition back to home care and off anticoagulant therapy received during the hospitalization period. Because the period of time after an inpatient or outpatient treatment for HF carries a higher risk for HF subjects[23,24], it would likely be a period where the benefit of rivaroxaban would be detected.

1.1.1. Compound Profile

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

Rivaroxaban is an oral, direct, FXa inhibitor anticoagulant. Rivaroxaban is rapidly absorbed after oral administration, with peak plasma concentrations occurring approximately 2 to 4 hours post dose. The elimination pathways of rivaroxaban include both hepatic and renal routes. The terminal elimination half-life of rivaroxaban is 5 to 9 hours in healthy young subjects (aged 20 to 45 years) and from 11 to 13 hours in healthy elderly subjects (aged 65 to 83 years). Due to rivaroxaban's multiple elimination pathways, there are few clinically relevant drug-drug interactions.

A randomized, multicenter Phase 1 study to evaluate the pharmacokinetics, pharmacodynamics, and safety of rivaroxaban (10 mg once daily) in subjects with acute (open-label, active-controlled) or chronic (double-blind, placebo-controlled) HF was recently conducted[12]. This study had 2 cohorts of subjects with HF (rivaroxaban was administered in addition to current congestive HF therapy), 8 subjects with acute decompensated HF (Cohort 1) and 18 subjects with chronic, stable, severe HF, NYHA Classes III or IV, (Cohort 2). The study was open-label, active-controlled (using enoxaparin as the control) in Cohort 1 and was double-blind, placebo-controlled in Cohort 2.

In general, the PK profile of rivaroxaban was comparable between the 2 cohorts. During steady state, peak plasma concentrations of rivaroxaban were reached between approximately 1 to 4 hours after administration, irrespective of cohort. Rivaroxaban was eliminated with a half-life of 7 to 8 hours, on average in both cohorts, which is comparable with data observed in healthy subjects (with a half-life of 5 to 9 hours). Compared with healthy subjects, clearance was decreased in subjects with HF. This resulted in, on average, approximately a 1.8-fold higher plasma exposure (AUC) in subjects diagnosed with HF (when considering both cohorts together) as compared with a pooled (single dose) database of healthy subjects (n=345 receiving a single dose of 10 mg rivaroxaban; age range: 18 to 80 years). Compared with healthy elderly subjects

(age range: 65 to 80 years with mean age: 71 years), AUC_{∞} was approximately 20% higher in subjects with HF.

The proportion of subjects reporting an adverse event or treatment-emergent adverse event was comparable between the rivaroxaban and placebo/enoxaparin groups and between the 2 cohorts.

In the Phase 3 ATLAS ACS 2 TIMI 51 study in which subjects with ACS were treated with rivaroxaban or placebo plus standard care antiplatelet therapy, 1694 subjects had a history of HF (etiology not specified) at baseline (rivaroxaban 2.5 mg b.i.d.: 562; rivaroxaban 5 mg b.i.d.: 574; placebo: 558). The composite endpoint event rate of CV death, MI or stroke was reduced in both rivaroxaban dose groups compared to placebo group with no apparent dose response (Table 1).

Table 1: Efficacy Endpoints in Subjects who had a History of Heart Failure at Baseline in the Phase 3 ATLAS ACS 2 TIMI 51 Study

	Rivaroxaban		Placebo	Hazard Ratio	
	2.5 mg b.i.d.	5 mg b.i.d.		Riva 2.5 mg vs. Placebo	Riva 5 mg vs Placebo
HF patients	(N=562)	(N=574)	(N=558)		
CV Death/MI/Stroke	59 (10.5%)	64 (11.1%)	96 (17.2%)	0.58 (0.42,0.81)	0.61 (0.44,0.83)
CV Death	23 (4.1%)	33 (5.7%)	50 (9.0%)	0.45 (0.27,0.74)	0.62 (0.40,0.96)
MI	36 (6.4%)	32 (5.6%)	50 (9.0%)	0.67 (0.44,1.03)	0.58 (0.37,0.91)
Stroke	7 (1.2%)	12 (2.1%)	10 (1.8%)	0.69 (0.26,1.81)	1.12 (0.48,2.61)

CV=cardiovascular; HF=heart failure; Riva=rivaroxaban; MI=myocardial infarction.
Source: ATLAS ACS 2 TIMI 51 Clinical Study Report and post hoc analysis of data from ATLAS ACS 2 TIMI 51.

The safety profile of rivaroxaban has been well established. As to be expected from a compound in the anticoagulant class of drugs, bleeding risk is associated with the use of rivaroxaban. Post hoc analysis showed that in this same subgroup of subjects with HF treated with rivaroxaban or placebo in ATLAS ACS 2 TIMI 51, the incidence of bleeding in the safety population for this subgroup was similar. The incidence of non-coronary artery bypass graft (CABG) TIMI major bleeding was 0.4%, 1.1%, and 0.5% in the rivaroxaban 2.5 mg group, the rivaroxaban 5 mg group, and the placebo group, respectively. The incidence of TIMI life-threatening bleeding was also similar at 0.4%, 0.5% and 0.5% in the rivaroxaban 2.5 mg group, the rivaroxaban 5 mg group, and the placebo group, respectively.

1.1.2. Heart Failure – Scope of the Problem

Heart failure is a major public health problem. In 2004 it was estimated that HF contributed to approximately 287,200 deaths in the US[22] and was the primary cause of death in approximately 57,000 patients based upon the most recent AHA statistics[21]. Heart failure is also the most common reason for hospitalizations in the US. The clinical and societal burden of heart disease consumes approximately 8.3% of the US health care budget and HF management is a major contributor of this burden. In addition, it has been estimated that there are about 6.5 million HF patients in Europe[25]. And if one looks at all the 51 countries represented by the European Society of Cardiology (with a population of 900 million people) there are an estimated 15 million patients with HF[8].

The numbers of HF patients are increasing due to the aging of the global population and the ability of increasing numbers of individuals to survive to an age when HF is likely to become a problem. In addition, the availability of improved medical technologies has enabled more effective treatment of ACS and conferred improved survival rates in patients following MI, the most powerful predictor of LV systolic dysfunction and risk of HF. As a result, the absolute numbers of individuals living with compromised cardiac function and clinical HF are expected to rise dramatically over the next few decades[25].

Heart failure is a complex disease in which poor cardiac reserve is the result of a complicated pathophysiology, which includes poor left ventricular (LV) function, derangement of the renin-angiotensin system, increased levels of sympathetic stimulation, and increased levels of cytokines and other inflammatory markers. Many of these can lead to a hypercoagulable state which is seen in HF. Despite advances made in the pharmacologic treatment of HF (ACE inhibitors, angiotensin receptor blockers [ARBs], beta blocker therapy, aldosterone inhibition), the mortality rate from severe HF remains at 60% within 5 years of diagnosis, and 50% of hospitalized patients with HF require readmission within 6 months of discharge[3].

1.1.3. Clinical Studies in Patients with Heart Failure with Anticoagulants

A number of approaches, including retrospective analyses of large HF studies such as SAVE, SOLVD, and V-HeFT, single and multicenter chart reviews, as well as prospectively defined, blinded interventional studies have attempted to address the question of whether anticoagulation can reduce the risk of important clinical events in patients with HF.

The EPICAL study was an observational study in a region of France that followed subjects admitted with severe HF and a LV dysfunction that was designed to evaluate treatment and prognosis. A post-hoc analysis of data from the 417 subjects in that study showed that the use of oral anticoagulants and/or aspirin was associated with 5-year survival rate that was better in subjects receiving anticoagulants than those who did not[11]. These results must be interpreted with caution as subjects were not randomized.

Retrospective Analyses

In the V-HeFT I study, the embolic rate in subjects receiving warfarin was similar to that in subjects who did not receive warfarin (2.9 v 2.7 events/100 patient-years; p =NS); V-HeFT II showed similar findings. In V HeFT I study, aspirin use was found to reduce the incidence of thromboembolism from 2.7 to 0.5 events/100 patient-years (p=0.007), whereas V HeFT II showed no significant reduction (2.1–1.6 events/100 patient-years; p=0.48[10].

The SAVE study reported an 81% risk reduction in stroke among subjects receiving warfarin. Aspirin reduced the overall risk of stroke by 56%, with a marked effect (66% risk reduction) in subjects with left ventricular ejection fraction (LVEF) <28% (p <0.001)[16].

An analysis of the SOLVD database indicated that warfarin use is associated with improved survival and reduced morbidity in subjects with HF. This association was primarily due to a

reduction in cardiac events[1]. In addition, the SOLVD investigators reported a 24% reduction in sudden death in subjects treated with aspirin monotherapy[9].

Prospectively Designed Studies

Four prospectively designed, randomized trials (WASH, WATCH, HELAS and WARCEF) have been conducted to assess the effect of anticoagulation or platelet inhibition on outcome in HF patients.

In the WASH study[5], HF subjects were randomized to receive warfarin, aspirin, or no antithrombotic therapy. Subjects had to have a clinical diagnosis of HF with evidence of LV dysfunction on echocardiogram (LVEF < 35%). This was an open label pilot study. The dose of aspirin was 300 mg/day and the mean INR was reported as 2.3. Time in therapeutic range (TTR) was not reported. A total of 279 subjects were randomized into the three arms of the study. No significant difference in the primary endpoint of death, non-fatal MI, or non-fatal stroke was seen, but there was a significant difference ($P < 0.05$) in all-cause hospitalization with subjects randomized to aspirin having the highest incidence. The study had poor recruitment felt to be due to a no antithrombotic arm.

The WATCH study[18] was a double-blind, double-dummy study comparing warfarin, aspirin at 162 mg/day, and clopidogrel 75 mg/day. Warfarin was titrated to an INR of 2.5 to 3.0. Subjects had symptomatic HF and an EF < 35%. The primary endpoint was the composite of all-cause mortality, MI, or stroke. The majority of subjects were NYHA Class III followed by Class II. Only 2% of subjects were Class IV. A total of 1587 subjects were randomized out of a planned 4500, and the study was terminated early. Because of low enrollment, the power to detect a 20% difference dropped from 90% to 41%. The TTR (acceptable INR range 2.0 to 3.5) for subjects on warfarin was 70%. There was no statistical difference in the comparisons made between warfarin and aspirin, warfarin and clopidogrel, or clopidogrel and aspirin. Hospitalization for HF was highest in the aspirin group (22.2%), followed by clopidogrel (18.5%) and warfarin (16.5%). Although hospitalization rates were higher in aspirin-treated subjects the absence of difference in survival or in the primary endpoint led the authors to avoid making any recommendations against the use of aspirin in patients with chronic HF in sinus rhythm.

The HELAS study[7] was a double-blind, placebo- and active- controlled study in subjects with either ischemic cardiomyopathy (IHD) or dilated cardiomyopathy (DCM). Those with IHD received either warfarin or aspirin, while those with DCM received either warfarin or placebo. The dose of aspirin was 325 mg/day while the warfarin was titrated to an INR of 2.0 to 3.0. Subjects were required to have symptomatic HF and a LVEF of < 35%. Although 6000 subjects were planned to be enrolled, only 197 were actually randomized due to slow enrollment. There were 115 subjects with IHD randomized, and 82 with DCM randomized. The primary endpoint was similar among the four groups, although deaths were lowest in the DCM group receiving warfarin.

The WARCEF study[13] had a targeted enrollment of 2860 subjects with HF. This was a double blind study comparing warfarin (target INR 2.0 to 3.5) to aspirin 325 mg/day. The objective of the study was to evaluate whether or not warfarin is superior to aspirin in the prevention of all-

cause mortality and all stroke (ischemic or hemorrhagic) in subjects with a LVEF ≤35%. The study was stopped prematurely due to low enrollment, and this resulted in a power of 67%. The study demonstrated that the rate of death, ischemic stroke or intracerebral hemorrhage was similar in the warfarin and aspirin groups (7.5% vs 7.9%, respectively). When the individual components of the primary endpoint are listed as separate components, it can be seen that, while death was not statistically different in either treatment arm, subjects receiving warfarin had a significantly lower rate of ischemic strokes than those receiving aspirin.

Table 2 summarizes the results of these four recent prospective HF studies. It should be noted in this table that the incidence of major bleeding was always highest in the warfarin treated subjects, ranging from 1.8% compared to 0.9% in the aspirin treated group in the WARCEF study to 5.2% versus 3.6% in the aspirin group and 2.1% in the clopidogrel group in the WATCH study.

All of these studies compared warfarin to either aspirin/clopidogrel, placebo, or both. There has been no large, randomized, controlled study comparing an anticoagulant plus antiplatelet therapy to antiplatelet therapy alone in addition to other standards of care.

Table 2: Summary of the Results Four Recent Prospective Studies in Patients with Heart Failure

Study	Treatment	N	Primary Endpoint	Primary Endpoint %			Hospitalization %[a]			Death %			Stroke %			Major Bleeding %		
				W	A	P/C[b]	W	A	P/C[b]	W	A	P/C[b]	W	A	P/C[b]	W	A	P/C[b]
WASH[5] (2004)	W vs A vsP	279	D/MI/CVA	26	32	26	47	64	48	35	30	21	0	2	2	4	1	0
WATCH[18] (2009)	W vs A vs C	1587	D/MI/CVA	19.6	20.7	21.6	16.5	22.2	18.5	17.0	18.0	18.3	3.9	2.7	2.5	5.2	3.6	2.1
HELAS[7] (2006)	W vs A (IHD); W vs P (DCM)	115; 82	D/MI/CVA; Hosp/PE	15.7; 8.9	14.9; -	**-;** 14.8	2.4; 4.4	3.2 -	-; 5.9	13.3; 3	9.6; -	-; 8.9	2.4; 0	2.1; -	-; 1.5	4.8; 4.4	0; -	-; 0
WARCEF[13] (2012)	W vs A	2305	D/CVA/ ICH	7.5	7.9	-	20.9	17.5	-	23.5	22.6	-	3	4.9	-	1.8	0.9	-

a) Hospitalization for all causes in WASH, and for HF hospitalization in WATCH, HELAS and WARCEF.
b) This column is placebo except in WATCH where it is clopidogrel and WARCEF where there was no placebo arm.
"-" indicates no data because of study design.
W=Warfarin; A=Aspirin; P=Placebo (or no antithrombotic agent); C=Clopidogrel; IHD= Ischemic cardiomyopathy group; DCM= Dilated cardiomyopathy group; D=death; MI=myocardial infarction; CVA=cerebrovascular accident; Hosp=hospitalization; PE =pulmonary embolism; ICH=intracerebral hemorrhage

1.2. Overall Rationale for the Study

Heart failure is a prothrombotic disease and thrombosis may be associated with increased morbidity and mortality. Although the results of previous studies with warfarin have demonstrated that anticoagulation is associated with reduced rates of important clinical events in patients with HF, results of these studies have not been conclusive[5,11,13,16,18]. Thus, a large prospectively designed study with a novel anticoagulant is warranted to adequately address whether or not rivaroxaban can reduce the risk of important clinical events in patients with HF and significant CAD.

The demonstration in the ATLAS ACS 2 TIMI 51 study that subjects with HF and a recent ACS have decreased rates of CV events and mortality with the use of rivaroxaban compared to placebo provides evidence for the exploration of rivaroxaban effects in similar patients with CAD but without a recent ACS event. Therefore, there is a strong rationale to investigate the use of rivaroxaban in addition to standard care in the patient population with HF and significant CAD. Patients who experience an exacerbation of HF are at higher risk of death within the first 6 months after discharge, with the greatest risk being in the first month. The most common cause is progression of HF, followed by sudden death. Due to its antithrombotic effect it is postulated that rivaroxaban will reduce CV death, MI, and stroke in this population.

Natriueretic peptides, whether BNP or NT-proBNP, have been shown to gauge the severity of decompensated HF and may help predict which subjects are at higher risk of future events for death or rehospitalization.[20,28] Thus, as of Amendment 1, all subjects will be required to have a minimum level of either BNP or NT-proBNP for entry into the study.

D-dimer data will be collected. D-dimer is a marker of coagulation and has been shown to be associated with increased mortality in subjects with chronic HF[17]. In a pharmacokinetic study of rivaroxaban in subjects with chronic HF, after 7 days of receiving rivaroxaban, D-dimer levels trended lower than baseline[12]. Blood for D-dimer levels will be drawn at baseline (Day 1) prior to the first dose of study drug from all subjects and at Week 4 from approximately 10% of subjects within each country to determine if rivaroxaban exerts any benefit in potentially high risk HF subjects. However, this biomarker is not sufficiently validated in this population to be used as an entry criterion that would identify a responsive treatment group.

The proposed study is designed to be a pivotal Phase 3 study, with adequate power to determine if the use of the FXa inhibitor rivaroxaban in addition to standard HF therapy can reduce the risk of important clinical outcome events (ie, all-cause mortality [ACM], MI, and stroke) in patients with HF and significant CAD following an episode of decompensated HF, defined as the “index event”. The addition of another therapeutic approach to reduce the risk of increased morbidity and mortality in HF patients would fulfill a substantial unmet medical need.

2. OBJECTIVES AND HYPOTHESES

2.1. Objectives

Primary Objective

- The primary objective is to demonstrate that rivaroxaban is superior to placebo in subjects with HF and significant CAD, who are receiving standard care, in reducing the risk of the composite of ACM, MI, or stroke following an index event.

Secondary Objectives

The secondary objectives are to compare rivaroxaban with placebo in addition to standard care in subjects with HF and significant CAD following an index event in reducing the risk of the following outcomes:

- Composite of CV mortality or re-hospitalization for worsening of HF
- CV mortality
- Re-hospitalization for worsening of HF
- Re-hospitalization for CV events

Exploratory Objectives

The exploratory objectives are to compare rivaroxaban with placebo in addition to standard care in subjects with HF and significant CAD following an index event in reducing the risk of the following outcomes:

- Selected medical resource utilization (MRU) data on re-hospitalization for CV events and for worsening of HF
- Symptomatic deep vein thrombosis (DVT)
- Symptomatic pulmonary embolism (PE)
- Benefit-risk balance

Safety Objectives

The safety objectives are to compare the following bleeding events with rivaroxaban and placebo in addition to standard care in subjects with HF and significant CAD following an index event:

- The composite of fatal bleeding or bleeding into a critical space (intracranial, intraspinal, intraocular [vitreous or retinal], pericardial, intra-articular, retroperitoneal, intramuscular (with compartment syndrome) with a potential for permanent disability
- Bleeding events requiring hospitalization
- Major bleeding events using the International Society on Thrombosis and Haemostasis (ISTH) bleeding criteria

Overall safety will also be assessed.

2.2. Hypothesis

The primary hypothesis of this study is that rivaroxaban 2.5 mg taken orally twice a day (in addition to standard care) is superior to placebo (in addition to standard care), in subjects with HF and significant CAD following an index event in reducing the risk of the composite of ACM, MI, or stroke.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter, event-driven, superiority study of rivaroxaban with clinical outcome assessments in subjects with HF (3 months or longer) and significant CAD. The subject population comprises men and women aged 18 and over who have a diagnosis of previous MI or significant CAD with a LV dysfunction (LVEF) ≤40%). Only subjects treated for decompensated HF will be eligible for enrollment. Eligible subjects must have an episode of decompensated HF (index event) requiring (a) an overnight stay in a hospital, emergency department, or medical observation facility with the capability of treating with intravenous medications and observing HF patients, or (b) an unscheduled outpatient visit to a HF management center, where parenteral therapy is required for HF stabilization. Subjects must also have a brain natriuretic peptide (BNP) level ≥ 200 pg/mL or N-terminal-proBNP (NT-proBNP) level ≥ 800 pg/mL (preferred assay) during the screening period and before randomization. Subjects have up to 30 days after discharge to be randomized if they are in stable condition.

The primary efficacy outcome is the composite of ACM, MI or stroke. The principal safety outcome is the composite of fatal bleeding, or bleeding into a critical space (intracranial, intraspinal, intraocular, pericardial, intra-articular, retroperitoneal, intramuscular with compartment syndrome) with a potential for permanent disability. Additional bleeding outcomes are bleeding events requiring hospitalization, and ISTH major bleeding events.

A total of 1,200 primary efficacy outcome events are targeted to demonstrate the superiority of rivaroxaban compared with placebo. A sample size of approximately 5,000 subjects will be randomized. If the event rate is lower than expected, the sample size may be increased by up to 500 subjects. Subjects who meet all of the inclusion and none of the exclusion criteria will be randomly assigned to receive rivaroxaban or placebo. Randomization will be stratified by country. After randomization, subjects will receive double-blind treatment (oral rivaroxaban 2.5 mg b.i.d. or matching placebo b.i.d.). All subjects will also receive standard care based on international clinical guidelines for HF and CAD as prescribed by their managing physicians. Standard care must include a diuretic (either on a routine or as needed basis) and renin angiotensin system (RAS) inhibitor/vasodilator therapy (ACE inhibitor, ARB or hydralazine/nitrates), and, unless contraindicated, beta blocker therapy, aldosterone antagonist therapy (where indicated), and aspirin/acetylsalicylic acid (ASA) (or other antiplatelet agent as appropriate). The dose of ASA should be 100 mg or less per day, unless not clinically appropriate. Dual antiplatelet therapy is allowed where indicated.

The study consists of a screening phase, a double-blind treatment phase, and a follow-up after the GTED, which is also the EOS visit, and the last contact with the subject. The screening phase may last up to 51 days before randomization (21 days maximum for a hospitalization admission plus up to 30 days after discharge from the facility treating the index event), followed by an estimated 6 to 54 months of double-blind treatment phase. The follow-up after the GTED is 30±15 days. The average duration of a subject in the study is expected to be approximately 29 months.

Subjects are expected to remain in the double-blind treatment phase until the sponsor-announced GTED. The date is based on site local time. The study sites will be notified of the GTED, at which time subjects will be instructed to discontinue study drug (after taking both their AM and PM doses on GTED) and return to the study site for the EOS visit (30±15 days, but no sooner than 15 days after the GTED). Efficacy and safety outcomes will be collected at the EOS visit.

Subjects who permanently discontinue the study drug before the GTED will complete the Early Permanent Study Drug Discontinuation visit as soon as possible after the last dose of study drug. In addition, these subjects should return for all scheduled visits, including the EOS visit. If these subjects refuse office visits, the investigator is asked to encourage the subjects to allow regular contact (eg, by telephone) until study end, according to the TIME AND EVENTS SCHEDULE, either with them, or with a close friend, relative, or their primary care physician to determine vital status and if an efficacy or safety outcome event has occurred.

A subject will be considered as having completed the double-blind treatment phase if the subject continues taking double-blind study drug until either the announced GTED or within 7 days before the death of the subject. If a subject experiences an outcome event such as MI or stroke, study drug may be temporarily held if necessary or if using other anticoagulant drugs or thrombolytic therapy. This also applies to events such as DVT or PE. After the appropriate treatment of the outcome event, the investigator may choose to resume study medication for the subject. However, study medication must be permanently discontinued for any intracranial hemorrhage or for any reason listed in Section 10.2.2.

Vital status will be collected for all subjects who permanently discontinue study drug early, withdraw from the study, or are lost to follow-up at the EOS visit either by telephone or in person, or if applicable, by a review of subject's medical or public records unless this contact is not allowed by local regulations.

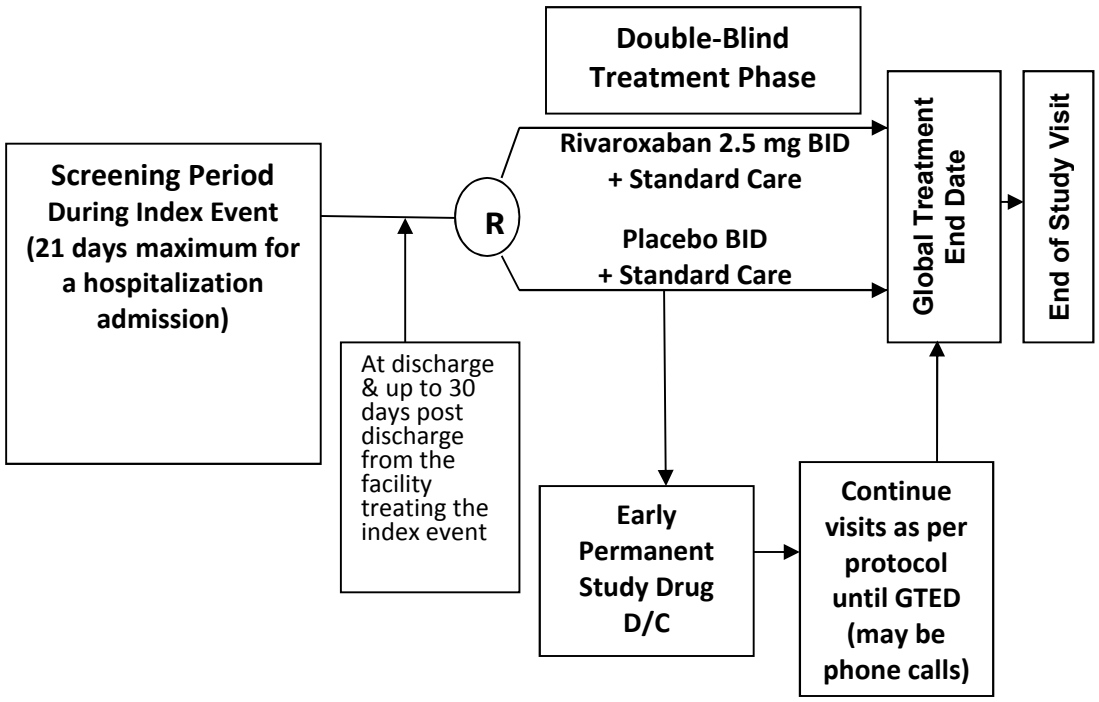
A blood sample for biomarker tests (D-dimer) will be collected at Baseline (Day 1) prior to the first dose of study drug from all subjects and Week 4 from 10% of randomly selected subjects within each country. An additional plasma sample from these subjects will be stored for up to 1 year after the end of the study for the possible assessment of additional biomarkers for exploratory review of the potential relationship between the markers and study outcome events.

A Steering Committee and an Independent Data Monitoring Committee (IDMC) will be commissioned for this study. Refer to Section 11.8, Independent Data Monitoring Committee,

for details. No independent Clinical Event Committee will be used for adjudication of outcome events in this study.

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

Figure 1: Schematic Overview of the Study Design (Study RIVAROXHFA3001)



BID=twice daily; D/C=discontinuation; GTED=Global Treatment End Date; HF=heart failure; R=randomization.

3.2. Study Design Rationale

Study Population

Patients with documented HF experience a high rate of CV death, MI, stroke, and thromboembolic events. These are important clinical events that profoundly impact patients, and constitute a large burden in terms of health care provision. Subjects with HF (3 months or longer) and significant CAD have been chosen because the addition of another therapeutic approach to reduce the risk of increased morbidity and mortality in these patients would meet an unmet medical need. The pharmacology, mechanism of action, and previous clinical studies of rivaroxaban suggest it will reduce the risk of the composite outcome. The timing of enrollment for these subjects (upon stabilization and at the time of discharge from the facility treating the index event) has been chosen because there is a high rate of mortality during this period, particularly during the first 2 months after discharge[23]. It is hypothesized that rivaroxaban, by reducing the thrombin burden, may help prevent cardiac events in this vulnerable population.

Blinding, Control, Study Phase/Periods, Treatment Groups

This randomized, double-blind, placebo-controlled, parallel-group, multicenter, event-driven design, is a scientifically rigorous approach for evaluating the efficacy and safety of rivaroxaban in subjects with HF (3 months or longer) and significant CAD, and meets the registration requirements for a superiority study.

Randomization will be used to avoid bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Randomization will be stratified by country. Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical outcomes.

The selection of a dose of 2.5 mg b.i.d. is based primarily on the results of the ATLAS ACS 2 TIMI 51 study, and the HF patient subgroup analysis where 2.5 mg b.i.d. of rivaroxaban resulted in benefit with an acceptable risk profile. Although these results were observed primarily on a background of dual antiplatelet therapy (ie, ASA plus clopidogrel) which is expected to represent about 10% of the subjects in the current study, the 2.5 mg b.i.d. dose has been selected for the following reasons:

1. There was no clear additional efficacy advantage for the 5 mg b.i.d dose with ASA only (Stratum 1) for the primary efficacy endpoint in either ATLAS ACS TIMI 46 (2.5 mg b.i.d.: HR [95% CI] 0.55 [0.23,1.3]; 5.0 mg b.i.d.: HR [95% CI] 0.69 [0.33,1.43]) or ATLAS ACS 2 TIMI 51 (2.5 mg b.i.d.: 27 events, HR [95% CI] 0.74 [0.45,1.22]; 5 mg b.i.d.: 24 events, HR [95% CI] 0.64 [0.38,1.07]) and therefore this dose is not being proposed for use after ACS.
2. Bleeding risk would be increased with 5 mg b.i.d, especially for subjects who are likely to be receiving antiplatelet therapy.

Placebo has been chosen as the comparator because all subjects should be receiving standard of care for their HF and significant CAD. This allows for the evaluation of efficacy and safety of rivaroxaban when added to standard care. In addition, there has been no well-controlled study to date that demonstrates any other oral anticoagulant in this population reduces mortality or CV events.

The length of the treatment period is not fixed; as the study is event-driven and subjects will continue treatment until the required number of primary efficacy outcome events (ie, 1,200) has been reached. This could be up to approximately 54 months, depending on the rates of enrollment and occurrence of primary efficacy outcome events.

Choice of Efficacy Measure

The choice of the primary efficacy outcomes is based on their use in prior rivaroxaban trials for primary and secondary prevention of cardiac events such as stroke, MI, or sudden CV death. These outcomes are considered acceptable and verifiable outcomes for the evaluation of prevention of CV events in HF patients with concomitant significant CAD[5,11,13,16,18].

While it is assumed that only CV death will be affected, ACM will be used as one of the outcome measures evaluated because: 1) the difference between ACM and CV death is expected to be minimal and, 2) it is an unimpeachable measure which requires no adjudication. The actual cause of death, however, will be collected.

Safety Assessment

The principal safety outcome will be the composite of fatal bleeding or bleeding into a critical space (intracranial, intraspinal, intraocular [vitreous or retinal], pericardial, retroperitoneal, intra-articular, intramuscular with compartment syndrome) with a potential for permanent disability.

Another bleeding outcome for this study will be bleeding requiring hospitalization. While this is not a standard scale used in recent trials, it will be able to help address the risk/benefit of using rivaroxaban in patients with HF.

In addition to these outcomes, data will be collected to allow for classification of major bleeding events using validated ISTH bleeding criteria.

Given the extensive background of existing safety data for rivaroxaban, only adverse events leading to discontinuation of study drug and non-CV serious adverse events will be collected and reported in this study. All CV events will be collected separately as study outcome events. Refer to Section 12.3.1, All Adverse Events for more details.

Biomarker Collection

Serum BNP or NT-proBNP level during the screening phase will be collected to determine enrollment eligibility. The use of serum BNP or NT-proBNP level is to exclude low risk subjects who may not have decompensated heart failure. Using natriuretic peptides (either BNP or NT-proBNP) in clinical decisions to make the diagnosis of HF is considered a Class I recommendation in the American College of Cardiology Foundation/American Heart Association guidelines and a Class IIa recommendation in the European Society of Cardiology guidelines[19,29].

Biomarker samples (D-dimer) will be collected at Baseline (Day1) prior to the first dose of study drug from all subjects and at Week 4 from 10% of randomly selected subjects within each country.

While D-dimer levels have been noted to be elevated in some HF patients[17] the association between elevated levels and morbidity and mortality is less clear. By collecting D-dimer it will allow analyses to be performed to determine if there is any correlation to outcome events in HF.

Benefit-Risk Analysis

Like other anticoagulant agents, rivaroxaban increases the risk of bleeding. To better understand the benefit of adding rivaroxaban to standard of care, a benefit risk assessment will be conducted by comparing the excess number of benefit events that are fatal or cause irreversible harm to that of risk events of comparable clinical impact. Because the baseline event rates vary between

different types of events, the comparisons of benefit and risk with different relative scales is difficult. Therefore, the evaluation is based on absolute risk difference, and the results are interpreted as the excess numbers of events after treatment of rivaroxaban for a certain period in a hypothetical patient population. The basis for these analyses is based on those used in publications by Unger[26] and Beasley et al[2].

Medical Resource Utilization and Health Economics

Treatment of HF with rivaroxaban may result in lower rates of CV re-hospitalization as well as the following selected utilization criteria: re-hospitalization for HF, overall CV and worsening HF re-hospitalization(s) length of stay (LOS), including emergency room (ER), intensive care unit (ICU) cardiac care unit (CCU) LOS and subject discharge destination.

4. SUBJECT POPULATION

The screening period for eligible subjects may last up to 51 days before randomization (21 days maximum for a hospitalization admission plus up to 30 days after discharge from the facility treating the index event).

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 into this 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.

1. Subject must be a man or woman 18 years of age or older.
2. Criterion modified per amendment
   - 2.1. Subject must have symptomatic HF for at least 3 months prior to screening.
3. Criterion modified per amendment
   - 3.1. Criterion modified per amendment
   - 3.2. Subjects must have an episode of decompensated HF (index event) requiring (a) an overnight stay in a hospital, emergency department, or medical observation facility with the capability of treating with intravenous medications and observing HF patients before randomization, or (b) an unscheduled outpatient visit to a HF management center, where parenteral therapy is required for HF stabilization. An episode of decompensated HF is defined as symptoms of worsening dyspnea or fatigue, objective signs of congestion such as peripheral edema or ascites, and/or adjustment of pre-hospitalization/outpatient visit HF medications. Subjects are eligible for randomization at discharge from the facility treating the index event and up to 30 days after discharge if they are in stable condition.

4. Criterion modified per amendment

   4.1. Subject must have a documented LVEF of less than or equal to 40% within 1 year before randomization. If more than one LVEF is available, the most recent one should be used, but it must be less than or equal to 40%. The ejection fraction will be determined by one of the following methods: echocardiogram, nuclear multigated acquisition (MUGA) scan, cardiac MRI, cardiac CT scan, or left ventriculography.

5. Subject must have evidence of significant CAD, defined as at least one of the following:

   - Documented previous MI
   - History of prior CABG
   - Coronary angiography demonstrating at least 50% stenosis of one or more arteries
   - History of percutaneous coronary intervention (PCI) with or without stent
   - Electrocardiogram (ECG) evidence (pathological Q waves) with corresponding wall motion abnormality on echocardiogram for those subjects with no documented history of MI, CABG, coronary angiogram or PCI

6. Criterion modified per amendment

   6.1. Criterion modified per amendment

   6.2. Subject must be medically stable in terms of their heart failure clinical status (defined as ambulatory and receiving no intravenous medications) at the time of randomization. The subject must be discharged from the facility treating the index event to a home environment. If transferred to a nursing home, rehabilitation center or other skilled facility, the stay must be 30 days or less so that the subject will be in a home environment at the time of randomization.

7. Criterion modified per amendment

   7.1. Subject must be receiving appropriate HF treatment at the appropriate dosing per guidelines:

   - Diuretic (required for study entry, but may be taken on an as needed basis)
   - Renin-angiotensin system (RAS) inhibitors such as an ACE inhibitor, or ARB, or vasodilator therapy such as hydralazine or nitrates if intolerant to ACE inhibitor and ARB (required for study entry)
   - Beta blocker therapy (if subject is not receiving beta blocker at randomization, it should be added and titrated during the study, unless not clinically appropriate)
   - Aldosterone antagonist therapy (if EF is less than or equal to 35%, but may also be added if the EF is greater than 35%, and titrated during the study)

   If subjects cannot be on all guideline based therapies, the reasons will be collected in the case report form (CRF).

8. Criterion modified per amendment

   8.1. Subject must be receiving appropriate CAD treatment per guidelines, which should include the following (where appropriate):

- Aspirin (ASA) at a dose of 100 mg or less per day unless not clinically appropriate.
- Clopidogrel, ticlopidine, prasugrel and ticagrelor are the only other antiplatelet agents that may be used concomitantly if clinically indicated. Dosing should be per labeling instructions.

9. Criterion modified per amendment

   9.1. Subject must have completed all prophylactic anticoagulation (such as enoxaparin, warfarin, heparin, etc) before randomization. Study drug should be started no sooner than 6 hours after the last dose of LMWH or UFH. In the event that subjects are receiving warfarin, the INR should be < 1.2 before the study drug is initiated.

10. Before randomization, a woman must be either:

    - Postmenopausal, defined as >45 years of age with amenorrhea for at least 18 months,
    - If menstruating:
      – If heterosexually active, practicing a highly effective method of birth control, including hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method [(eg, condoms, diaphragm, or cervical cap, with spermicidal foam, cream, or gel)], or male partner sterilization, consistent with local regulations regarding use of birth control methods for subjects participating in clinical studies, for the duration of their participation in the study, or
      – Surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal ligation, or otherwise be incapable of pregnancy), or
      – Not heterosexually active

    Women must agree to continue using these methods of contraception throughout the study. Women using oral contraceptives must agree to use an additional birth control method.

11. A woman of childbearing potential must have a negative serum or urine pregnancy test before randomization occurs.

12. Criterion deleted per amendment

13. Criterion modified per amendment

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

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

15. 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, including follow-up. (Follow-up is intended to continually assess the vital status and any outcome events in subjects who prematurely discontinue from study drug.)

16. Criterion modified per amendment

    16.1. Subjects must have a minimum level of 200 pg/mL BNP or 800 pg/mL NT-proBNP (preferred assay) during the screening period and before randomization.

4.2. Exclusion Criteria

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

1. Subject has a bleeding risk: Any condition that, in the opinion of the investigator, contraindicates anticoagulant therapy or would have an unacceptable risk of bleeding, such as, but not limited to, the following:
    - Active internal bleeding
    - Clinically significant bleeding, bleeding at a noncompressible site, or bleeding diathesis within 28 days of randomization
    - Platelet count <90,000/µl at screening
    - History of intracranial hemorrhage
    - Major surgery, biopsy of a parenchymal organ, or serious trauma (including head trauma) within 28 days before randomization
    - Sustained uncontrolled hypertension: systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥100 mmHg
2. Criterion modified per amendment

    2.1. Subject has a severe concomitant disease such as:

    - Atrial fibrillation (AFib) or another condition that requires chronic anticoagulation (subjects with isolated transient AFib may be allowed at the discretion of the treating physician investigator)
    - Documented acute MI during index event
    - Planned cardiac surgery within 28 days either prior to or after randomization, excluding PCIs and electrophysiologic devices
    - Implantation of an electrophysiologic device such as implantable cardioverter defibrillator or pacemaker planned to occur within 14 days either prior to or after randomization
    - Planned cardiac transplantation or mechanical ventricular assist device implantation
    - Known history of severe valvular disease that is significantly contributing to the heart failure (eg, aortic stenosis with a gradient of >40 mmHg or mitral regurgitation with regurgitant fraction ≥60%)
    - Chronic episodes of ventricular tachycardia (sustained > 30 seconds and any ventricular tachycardia associated with symptoms)

- Heart failure due to the following causes: postpartum, infectious (eg, HIV, acute myocarditis), substance abuse (eg, cocaine), alcohol, infiltrative disease (eg, amyloidosis), or a transient reversible condition (eg, thyrotoxicosis, arrhythmia)
- Cardiogenic shock at the time of randomization
- Estimated glomerular filtration rate (eGFR) <20 mL/min (MDRD method, See Attachment 1) at screening or if dialysis is anticipated within 6 months from screening
- Active malignancy or other condition, other than underlying HF, limiting life expectancy to less than 6 months
- Acute endocarditis
- Currently treated with hemofiltration or dialysis
- Known significant liver disease (eg, acute hepatitis, chronic active hepatitis, cirrhosis, hepatic disease which is associated with coagulopathy, moderate or severe hepatic impairment [corresponding to Child-Pugh B or C])
- Anemia (ie, hemoglobin <8 g/dL) at screening
- Known history of severe peptic ulcer disease (ie, history of at least 2 episodes of upper gastrointestinal bleeding)
- History of severe thrombocytopenia (platelet count < 50,000/µl)
- Known clinical history of HIV

3. Subject had a prior stroke within 90 days of randomization.
4. Subject has been hospitalized longer than 21 days during the index event. The date of admission is considered the first day of hospitalization and the date of discharge is considered the last day of hospitalization.
5. Subject has known allergies, hypersensitivity, or intolerance to rivaroxaban or its excipients (refer to Investigator's Brochure).
6. Planned intermittent outpatient treatment with positive inotropic drugs administered intravenously.
7. Subject is currently receiving and has the intention to continue any disallowed therapies as noted in Section 8, Prestudy and Concomitant Therapy.
8. Subject has received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 28 days before the planned first dose of study drug or is currently enrolled in an investigational study.
9. Subject is a woman who is pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study.
10. Subject 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.

11. Subject is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.
12. At the time of screening, subject will not consider allowing a telephone contact to determine any outcome events and/or vital status, up until the end of the study should they prematurely discontinue study drug.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. Hospital/local laboratory results and imaging studies (within 51 days [21 days maximum for a hospitalization admission plus up to 30 days after discharge from the facility treating the index event]) will be used for screening purposes and will serve as the baseline (Day 1) laboratory results. There must also be documentation of CAD and HF symptoms (such as EF ≤40% within 1 year). The laboratory results closest to the randomization date should be used. The date of the laboratory tests will be collected on the electronic case report form (eCRF). If a subject's status changes (including laboratory results or receipt of additional medical records) after screening but before 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. The screening pregnancy test, if needed, should be collected on Day 1, prior to randomization and verified as negative for eligibility. 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. A woman of childbearing potential who is heterosexually active must remain on a highly effective method of birth control (see Section 4.1, Inclusion Criteria).
2. Criterion modified per amendment

   2.1 Criterion modified per amendment

   2.2 Subjects may not take any additional anticoagulant(s) (antiplatelet agents ASA, clopidogrel, prasugrel, ticlopidine or ticagrelor are acceptable) concomitantly with study medication. Subjects who develop any condition which requires permanent or long term anticoagulation (eg, DVT, atrial fibrillation [$CHADS_2$ = 2 or higher]) will be discontinued from study drug.
3. Criterion modified per amendment

   3.1 Prasugrel is prohibited in subjects who are ≥75 years old in age, or in subjects with prior TIA or stroke.
4. Nonsteroidal anti-inflammatory agents (NSAIDs) may be used on a temporary basis, but should be avoided for chronic use during the study period.
5. Criterion modified per amendment

   5.1 Strong inhibitors of cytochrome P450 3A4, such as but not limited to, ketoconazole, itraconazole, telithromycin, clarithromycin and voriconazole or protease inhibitors, are

prohibited as concomitant therapy within 4 days before randomization, or during the study.

5.2 Criterion added per amendment

5.2.1 Any drug which is contraindicated in patients with heart failure (eg, cilastazol)

6. Strong inducers of cytochrome P450 3A4, such as but not limited to, rifampin/rifampicin, rifabutin, rifapentin, phenytoin, phenobarbital, primidone, St. John's Wort, or carbamazepine, are prohibited as concomitant therapy within 4 days before randomization, or during the study.
7. Proton pump inhibitors may be used, however subjects receiving clopidogrel should not receive omeprazole or esomeprazole.
8. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a subject into the study.
9. A man who has not had a vasectomy and is sexually active with a woman of childbearing potential must use a double-barrier method of birth control (see Section 4.1, Inclusion Criteria). All men must also not donate sperm until last dose of study drug.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Subjects will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by country. The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject. User identification information must not be shared.

Approximately 10% of subjects within each country will be randomly selected from whom Week 4 D-dimer data will be collected. The IWRS will announce if a subject is selected when the subject is randomized to study treatment.

Blinding

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

Data that may potentially unblind the treatment assignment (ie, events that contribute to the primary and secondary outcomes, treatment allocation, or other specific laboratory data such as all D-dimer results) will be handled with special care to ensure that the integrity of the blind is

maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding. In addition, eGFR will be calculated by the IWRS to ensure eligibility at screening.

Under normal circumstances, the blind should not be broken until all subjects have completed the study and the database is finalized. The blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the treatment by contacting the IWRS. It is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented by the IWRS in the source document. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner.

To most effectively preserve clinical study integrity, the treatment assignment of events that contribute to the primary and secondary outcomes will remain blinded until the study is completed and the database locked. In this way bias is reduced and a truly double-blind, placebo-controlled investigation can be carried out. As the events of CV death, MI, stroke, symptomatic DVT, and symptomatic PE are considered efficacy outcomes, they will not be reported as adverse events or serious adverse events (see Section 12.3.1, All Adverse Events for more details).

Subjects who have had their treatment assignment unblinded may continue on study drug unless the subject meets a study drug discontinuation criterion. Investigators should not disclose treatment assignment to the subject whenever possible, even in a special situation where the treatment assignment has been unblinded to the investigator.

An IDMC will review safety data periodically. The IDMC will not be involved with the study otherwise. Therefore, unblinded review of safety data by anyone else is unnecessary. IDMC responsibility and procedures are outlined in Section 11.9, Interim Analysis. More details will be provided in the IDMC charter.

6. DOSAGE AND ADMINISTRATION

Treatment groups: rivaroxaban and placebo. Subjects will be randomly assigned in a 1:1 ratio to receive oral rivaroxaban 2.5 mg b.i.d. or placebo b.i.d. (each in addition to standard of care for HF and CAD as prescribed by their managing physician).

All subjects will receive study drug (rivaroxaban or placebo) orally twice daily; once in the morning and once in the evening, with or without food, at approximately the same times each day throughout the study. The first dose of study drug should be taken in the clinic by the subject on the day of randomization. If the first dose is taken prior to or at 12:00 pm (noon), it is considered the AM dose of the day and a PM dose should also be taken. If it is taken after

12:00 pm (noon), it is considered the PM dose of the day and another pill should not be taken that day. Once the GTED is reached, all subjects currently receiving blinded study drug should discontinue study drug (after taking both their AM and PM doses on GTED) and complete the EOS visit (refer to TIME AND EVENTS SCHEDULE).

Throughout the study, study drug will be dispensed at appropriate intervals (see the TIME AND EVENTS SCHEDULE) to ensure that subjects have adequate quantities of study drug between study visits. In addition, study site personnel will instruct subjects on how to store study drug for at-home use as indicated for this protocol. For rivaroxaban tablets, no storage restrictions (temperature, humidity, light) apply. The storage recommendation for rivaroxaban is at room temperature (approximately 15° to 30°C).

Interruption of Study Drug

Study drug may be interrupted (see Section 10.2.1, Temporary Discontinuation of Study Treatment) as necessary for invasive procedures or as medically needed (eg, in the setting of a bleeding event or a required prohibited therapy).

A missed dose should be taken as soon as possible (no later than 6 hours after the scheduled dosing time), and the next scheduled dose should be taken at the regular time. If >6 hours have elapsed after the scheduled time the dose should be skipped and the next dose should be taken at the regular time. An occasional forgotten dose need not be recorded. Intentional stopping of study drug by the subject, unintentional stopping of study drug for more than 7 consecutive days, or direction to temporarily stop study drug by the investigator or other physician will be documented and recorded in the eCRF.

7. TREATMENT COMPLIANCE

The IWRS system will keep track of study drug dispensed to the subjects. Subjects will return empty study drug containers and unused study drug at those visits when a new supply of study drug is to be received.

Study drug accountability will be performed at each visit. Subjects should report any unintentional interruption or missed doses of 7 consecutive days or more to the study-site personnel at each visit. It is understood that subjects may occasionally miss a dose or that a subject may be placed on temporary discontinuation (see Section 10.2.1, Temporary Discontinuation).

8. PRESTUDY AND CONCOMITANT THERAPY

For each subject, the drug identity of all CV therapies, proton pump inhibitors, antiplatelet agents, anticoagulants and ASA use taken during the index event through the end of the study will be recorded on the appropriate page of the eCRF. Relevant concomitant medications or treatment (eg, antibiotics for sepsis or surgical interventions) given for adverse events and use of other prohibited therapies, as specified below, will also be documented on the appropriate page of the eCRF.

Required/Allowed Therapies

- Subjects must be receiving at a minimum for their HF: a diuretic on a routine or as needed basis, and RAS inhibitor/vasodilator therapy (either an ACE inhibitor, ARB, or hydralazine/nitrate combination), and, unless contraindicated, the following:
    - Beta blockers, which should be titrated to the maximum dose recommended by current guidelines, unless not clinically appropriate. (If beta blockers are not prescribed, or the dose is lower than recommended, the reason will be noted in the eCRF)
    - Aldosterone antagonists, which should be prescribed per guideline recommendations. (If aldosterone antagonists are not prescribed, or the dose is lower than recommended, the reason will be noted in the eCRF)
    - Additional standard care treatments for HF and CAD (except anticoagulants) as prescribed by their managing physician are allowed.
- Subjects should be receiving antiplatelet therapy as standard care for their CAD. This would include aspirin (ASA) up to 100 mg/day, unless not clinically appropriate. Clopidogrel, ticlopidine, and ticagrelor may be used if indicated. Prasugrel may also be used if indicated, but not in subjects with a prior history of TIA or stroke or those who are 75 years of age or older. There is limited data on the combined use of rivaroxaban with either ticagrelor or prasugrel. The IDMC will monitor any increased risk to the subjects in this study using these combinations. The use of clopidogrel, ticlopidine, ticagrelor, or prasugrel should be prescribed according to the approved labeling for each drug.
- Antiarrhythmic therapy is allowed.
- Digoxin is allowed.

Prohibited Therapies

At each visit prohibited medications and the duration of use will be recorded on the eCRF. NSAID therapy should be recorded if greater than two weeks during the interval between visits.

Nonsteroidal anti-inflammatory agents may be used on a temporary basis, but should be avoided for chronic use during the study period.

Strong inhibitors of cytochrome P450 3A4, such as but not limited to, ketoconazole, itraconazole, telithromycin, clarithromycin and voriconazole or protease inhibitors, are prohibited as concomitant therapy within 4 days before randomization, or during the study.

Strong inducers of cytochrome P450 3A4, such as but not limited to, rifampin/rifampicin, rifabutin, rifapentin, phenytoin, phenobarbital, primidone, St. John's Wort, or carbamazepine, are prohibited as concomitant therapy within 4 days before randomization, or during the study.

Any drug which is contraindicated in patients with heart failure (eg, cilastazol) is prohibited.

Proton pump inhibitors may be used, however subjects receiving clopidogrel should not receive omeprazole or esomeprazole. Use of other proton pump inhibitors is allowed.

Antiplatelet therapy other than aspirin (ASA), clopidogrel, ticlopidine, prasugrel, or ticagrelor is prohibited. Prasugrel is prohibited in subjects who are ≥75 years old in age, or in subjects with prior TIA or stroke.

Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a subject into the study.

Also refer to Section 4.3 for additional prohibited therapies.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The TIME AND EVENTS SCHEDULE summarizes the frequency and timing of efficacy, MRU, and safety measurements applicable to this study.

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

The following MRU data will be collected in all subjects during each study visit: CV re-hospitalization, re-hospitalization for HF, overall CV and worsening HF re-hospitalization(s) LOS, including LOS in ER, ICU, and CCU and subject discharge destination.

Additional laboratory screening tests are not expected to be performed by the investigator as these will likely be part of their index event evaluation. If available during the index event, the value of creatine kinase-muscle and brain subunit (CK-MB), troponin, levels should be recorded in the local lab section of the eCRF (if more than one test values are available, use the highest value). In addition to the hemoglobin collection required at screening, subjects will be required to have a local lab hemoglobin collected at Week 12 (±14 days); if not collected at Week 12, it should be done no later than Week 24 (+ 14 days). Approximately 3-5 mL of blood will be required for the hemoglobin test. In the event that an additional screening lab test is required for enrollment, the maximum total blood volume to be collected from such subject will be approximately 20 mL, and will be processed locally. Blood for BNP or NT-proBNP measurements will be drawn prior to randomization as part of the inclusion criteria. If available, BNP or NT-proBNP will be measured by the local hospital laboratory. If local measurements of BNP or NT-proBNP are not available, approximately 5 mL of blood will be sent to a local central laboratory for measurement of BNP or NT-proBNP (whichever is available at that laboratory). In addition, the D-dimer laboratory tests will be performed per study protocol. Approximately 3 mL of blood will be required for each D-dimer test (Baseline, Week 4 [if applicable]).

Information concerning the proper collection, handling and shipping of D-dimer samples can be found in the laboratory manual provided to each study site.

9.1.2. Screening Phase

The screening period may last up to 51 days before randomization (21 days maximum for a hospitalization admission plus up to 30 days after discharge from the facility treating the index event). Subjects must be randomized only after discharge. Subjects will be screened using local laboratory results for the inclusion and exclusion clinical laboratory parameters, and these values will also serve as baseline (Day 1) laboratory values.

9.1.3. Double-Blind Treatment Phase

Day 1/Day of Randomization

Performance of the screening procedures may extend into Day 1 of the double-blind treatment phase, as long as all procedures are completed before randomization on Day 1. If the subject meets all of the inclusion and none of the exclusion criteria, he or she is eligible to be randomly assigned to receive rivaroxaban or placebo. All screening activities must be completed before randomization and the results must be available to the investigator for review to ensure that no exclusion criteria are present.

Treatment Visits

Subjects will be instructed to return to the study site according to the visit schedule in the Time and Events Schedule.

Unscheduled Visit

Subjects should be seen by the investigator between scheduled visits for reasons such as:

- Adverse event, based upon the severity and clinical judgment of the investigator
- Lost medication requiring replacement
- Reported outcome event
- After a discharge for any re-hospitalization

Early Study Drug Discontinuation/Early Withdrawal from Study

If a subject permanently discontinues treatment before the end of the double-blind treatment period (ie, the GTED), the subject should complete the Early Permanent Study Drug Discontinuation procedures (see TIME AND EVENTS SCHEDULE). Because the primary analysis of the study is based upon the intent-to-treat population (ITT), the subject should return for all subsequent site visits and procedures until the EOS visit. It is imperative for the integrity of the trial and results to have ongoing outcome event and vital status ascertainment. If a subject is unwilling or unable to return for follow-up visits in person, sites should collect as much follow-up visit information as possible, including contacting the subject by telephone or by mail to determine vital status and if an outcome event has occurred, as agreed to by the subject during the initial informed consent process. If applicable, vital status may be obtained by reviewing the subject's medical or public records unless this contact is not allowed by local regulations.

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

If a subject temporarily discontinues study drug, and the GTED is announced prior to the subject resuming study drug, the subject will then be considered to have been permanently discontinued from study drug. The Early Premature Study Drug Discontinuation Visit and EOS Visit for this subject will occur on the same day.

9.1.4. Follow-up after GTED

The date when the targeted number of primary outcome events are predicted to have occurred will be known as the GTED. The sponsor will notify all investigative sites of the GTED. The sites should contact all subjects and instruct them to stop study drug on the GTED (after taking both their AM and PM doses on the GTED) and schedule the EOS visit (30±15 days, but no sooner than 15 days after the GTED). A visit is not necessary on GTED. All subjects who discontinued study drug early (and are not taking study drug at the time of the GTED) should also complete the EOS visit within the same time frame after the GTED.

9.2. Efficacy

9.2.1. Efficacy Evaluations

At each visit during the study, the investigator will evaluate the subject for the occurrence of the following efficacy outcome events:

- Death
- Myocardial infarction (MI)
- Stroke
- Symptomatic PE
- Symptomatic DVT
- CV and HF re-hospitalization

The investigator will use all available medical records (including hospital records, discharge summaries, consultant reports, imaging reports, local laboratory results, an autopsy report, and a death certificate) to determine if an outcome event has occurred for a particular subject. Copies of these documents must be part of the source documentation for any subject with an outcome event in order to verify the outcome event. Transient ischemic attack (TIA) is not an outcome event. The date of the TIA should be entered in the eCRF.

The investigator will use his/her medical judgment based upon the definitions below to determine if an event has occurred. A manual further delineating the definitions of events will be provided to each investigator's site. The criteria below list documents which must be available to the investigator and in the source document to confirm an event. These documents will be maintained in the source file and will be verified by the local study monitors. If the study

monitor is unable to determine if the source documents are sufficient, the determination will be escalated to the Local Trial Manager, or a Country Outcome Advisor, who is an independent physician not associated with this study. The sponsor's clinical group will ensure that all the appropriate documents from the investigative site are available and reviewed. All source documents and reviewers will remain blinded. These procedures will be outlined in a separate document.

Except for death, an outcome event may not be based on only information verbally obtained. The information must be verified by documents listed below for each outcome event. While information about a death may be obtained verbally, additional documentation should be obtained to classify the cause of death.

The investigator should complete the appropriate eCRF pages as soon as information is received regarding an outcome event.

Outcome Event Definitions

Death

Death will be documented as either: Cardiovascular, or Non-Cardiovascular, or with Unknown Cause. CV and non-CV deaths should be documented by one of the following:

- Hospital discharge summary
- Death certificate
- Autopsy report
- Written communication with the treating physician

Cardiovascular Death

Any death that is not clearly non-CV will be considered a CV death. For example, CV death includes deaths due to spontaneous bleeding, MI, stroke, worsening heart failure and arrhythmias. Cardiovascular death would include death due to CV procedures and sudden death. Sudden death would include any death in which there is abrupt collapse and death during which time no other evaluation is made either with ECG monitoring, imaging, or other laboratory testing. Unwitnessed death is one in which the subject is discovered dead after last having been seen in a stable state. An unwitnessed death would not include death from a chronic, deteriorating non-CV illness such as cancer. A death caused by traumatic bleeding would not be considered a CV death.

Non-Cardiovascular Death

Any death clearly not related to a CV cause, such as infection, trauma, or cancer.

Death with Unknown Cause

If no information is available regarding the cause of death (other than an oral communication from a relative, acquaintance, or representative without any information regarding the immediate cause provided) the cause of death will be classified as unknown.

However, the investigator should record efforts made to obtain information of the cause of death in the source documents.

Myocardial Infarction

In the absence of a PCI or CABG, the subject must have at least 2 of the following criteria to document an MI:

- Elevated cardiac biomarkers (troponin I or T, or creatine kinase-muscle and brain subunit [CK-MB]) greater than the hospital/local lab's upper limit of normal (ULN)
- Development of new pathological Q waves in at least 2 contiguous leads on the ECG
- New significant ST changes of either new ST elevation at the J-point in 2 contiguous leads, or new horizontal of downsloping ST depression in 2 contiguous leads
- New left bundle branch block (LBBB)
- Autopsy confirmation (this alone is sufficient)
- Cardiology consultation report or discharge summary clearly stating a MI has occurred (If the abnormal cardiac biomarker laboratory results are mentioned in the reports, this will count as two criteria)

If a subject undergoes PCI, the subject must meet 2 of the criteria below to document a post-procedure MI:

- Elevated cardiac biomarkers (troponin I or T, or CK-MB) >5 x the hospital/local lab's ULN for samples obtained within 48 hours of the procedure if the baseline values were normal, plus either prolonged ischemia (> 20 minutes of chest pain), ischemic ST changes or new pathological Q waves, or angiographic evidence of a flow-limiting complication, or imaging evidence of new loss of viable myocardium or new regional wall abnormality
- Development of new pathological Q waves in at least 2 contiguous leads on the ECG
- Cardiology consultation report or discharge summary clearly stating a MI has occurred (If the abnormal cardiac biomarker laboratory results are mentioned in the reports, this will count as two criteria)

After CABG surgery, the subject must meet 1 of the criteria below to document an MI:

- Elevated cardiac biomarkers (troponin I or T, or CK-MB) >10 x the hospital/local lab's ULN for samples obtained within 48 hours of the procedure with development of new pathological Q waves or a new LBBB on the ECG, or angiographic documented new graft or new native coronary artery occlusion, or imaging evidence of new loss of viable myocardium or new regional wall abnormality
- Cardiology consultation report or discharge summary clearly stating an MI has occurred (If the abnormal cardiac biomarker laboratory results are mentioned in the reports, this will count as two criteria)

Stroke

Stroke is defined as a new, sudden, focal neurological deficit resulting from a presumed cerebrovascular cause that is not reversible within 24 hours and not due to a readily identifiable cause such as trauma, a tumor or seizure.

If an event matching this definition lasts less than 24 hours it will be considered a TIA.

All suspected strokes (including TIA) will require source verification that will become part of the subjects source file. Subjects in whom a stroke is diagnosed must have at least two of the following criteria:

- Autopsy confirmation (this alone is sufficient)
- Clinical signs of a stroke which include a focal neurologic deficit which was not present at the last visit (The deficit may include hemiparesis, aphasia, apraxia, dysphagia, cortical blindness, or ataxia)
- Imaging study (MRI or CT scan of head and brain) within two weeks after the onset of symptoms that demonstrates a stroke corresponding to the clinical signs and symptoms
- Neurology consultation report indicating the occurrence of a stroke
- Hospital discharge summary indicating the occurrence of a stroke
- Investigator detecting a difference in the neurologic status of the subject which indicates a stroke since the previous visit (If no imaging is performed, the investigator's examination must be corroborated by a neurologic consultation)

Investigators will further classify the strokes based upon imaging studies.

- Primary ischemic infarction – stroke without focal collections of intracranial blood [The occurrence of hemorrhagic conversion of a primary ischemic infarction will be recorded only if there are two or more imaging studies demonstrating progression of the stroke from ischemic (or bland) to hemorrhagic]
- Primary hemorrhagic – stroke with focal collections of intracerebral blood (The diagnosis of primary hemorrhagic stroke can only be made with imaging studies. It may include intraventricular hemorrhage)
- Subarachnoid hemorrhage – the diagnosis requires documentation by imaging study
- Uncertain – no imaging or autopsy available

A Rankin evaluation using the Modified Rankin Scale (Attachment 2) will be obtained by the investigator or designee between 6-18 weeks following a stroke or at EOS, whichever occurs first.

Other events of intracranial bleeding which will not be considered as strokes as they are usually traumatic in nature are:

- Subdural hematoma
- Epidural hematoma

These also require documentation by imaging studies and will be recorded on the bleeding event eCRF page.

Symptomatic PE

A PE is diagnosed only if the subject has symptoms of PE such as sudden onset of dyspnea, chest pain, or fainting, and one of the following criteria are met:

- Autopsy confirmation (this alone is sufficient)
- High probability ventilation/perfusion lung scan
- Intermediate probability ventilation/perfusion lung scan with a positive D-dimer test
- Positive spiral CT scan of the chest
- Positive pulmonary arteriogram

Symptomatic DVT

A symptomatic DVT will be diagnosed if the following criteria are met:

- Pain, swelling, or other symptoms of DVT in the extremity in question
- Positive compression ultrasound **OR** positive venogram

Re-Hospitalization for Worsening of Heart Failure

Hospitalization for worsening HF requires that subjects be hospitalized (as an inpatient, in emergency department, or in a medical facility with the capability of treating with intravenous medications and observing patients with HF) for an overnight stay or longer, and meet at least 3 of the following criteria:

- Symptoms of dyspnea or fatigue
- Objective signs of congestion such as worsening edema, ascites, or rales
- Treatment with intravenous diuretics or inotropic agents
- Adjustment of pre-hospitalization HF medication
- Discharge summary listing worsening HF as the primary reason for admission

The primary reason for hospitalization may not be a non-CV event (e.g., infection, cancer, non-CV surgery. The investigator will use his/her clinical judgment to determine if the primary diagnosis for a re-hospitalization supports worsening HF or if the admission is caused by a different cardiovascular event occurring concurrently (e.g., cardiac arrhythmia). If the primary reason for the re-hospitalization could be either event, the default should be re-hospitalization for worsening HF.

Re-Hospitalization for a CV Event

Hospitalization for a CV Event requires that subjects be hospitalized (in-patient or emergency department) for greater than 24 hours and must meet the following criterion:

- Discharge summary with primary reason for admission listed as CV in nature (e.g., bleeding, arrhythmia, ACS, MI) other than HF which is captured in the HF re-hospitalization

The primary reason may not be a non-CV event (e.g., infection, cancer, non-CV surgery).

MI, Stroke, DVT, PE, and spontaneous bleeding events are considered cardiovascular events. If any of these are the primary reason for a hospitalization, complete both a re-hospitalization for CV event form and the outcome event eCRF form.

9.2.2. Efficacy Outcomes

Primary Efficacy Outcomes

The primary efficacy outcome is the composite of ACM, MI, or stroke.

Secondary Efficacy Outcomes

The secondary outcomes include:

- Composite of CV mortality and re-hospitalization for worsening of HF
- CV mortality
- Re-hospitalization for worsening of HF
- Re-hospitalization for CV events

Exploratory Efficacy Outcomes

- Selected MRU data on re-hospitalizations for CV events and for worsening of HF
- Symptomatic DVT
- Symptomatic PE

9.3. Biomarkers

Serum BNP or NT-proBNP level during the screening phase will be collected to determine enrollment eligibility.

Biomarker samples will be collected for evaluation of D-dimer from all subjects at randomization, prior to the first dose of study drug. In addition, samples of D-dimer will be collected randomly from 10% of subjects within each country at Week 4. When a subject is randomized to treatment assignment at the randomization visit, the IWRS will specify if the subject is among the biomarker subset at Week 4.

9.4. Medical Resource Utilization

Medical Resource Utilization data collection will include: re-hospitalization for CV and HF causes, overall CV and worsening HF re-hospitalization(s) LOS, including LOS in ER, ICU, and CCU and subject discharge destination.

9.5. Safety Evaluations and Outcomes

9.5.1. Safety Evaluations

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

Bleeding Outcome Evaluations

The following will be collected for subjects with bleeding events requiring medical attention, hospitalization, or permanent study drug discontinuation, and entered on the eCRF bleeding event page. Bleeding events are not reported as adverse events (see Section 12.3.1 All Adverse Events for further instruction):

- Location of the bleeding. Bleeding sites will be entered on the eCRF for all reported bleeding events, including any bleeding into a critical space (intracranial, intraspinal, intraocular, pericardial, intra-articular, retroperitoneal, intramuscular with compartment syndrome) with a potential for permanent disability.
- If the bleeding causes hospitalization (or prolongs hospitalization) it will be noted on the eCRF (Note that bleeding events will not be captured as adverse events or serious adverse events except for traumatic bleeding events resulting in death). Non-traumatic bleeding events are considered CV in origin. If non-traumatic bleeding is the primary reason for a greater than 24 hour hospitalization, a re-hospitalization for CV Event eCRF page must also be completed. In addition, a discharge summary indicating the primary reason for admission as bleeding is required.
- Fatal bleeding will be collected. A fatal bleeding event is one in which the subject dies within 7 days of a bleeding event requiring hospitalization or ISTH major bleeding.
- For subjects hospitalized for a bleeding event, the admission hemoglobin and the lowest hemoglobin, or hematocrit (if hemoglobin is not available) will be entered on the eCRF as well as the final hemoglobin or hematocrit closest to discharge.
- Transfusion with blood or blood products will be recorded.

Bleeding Event Assessment and Classification

The study will use the ISTH Bleeding Event Classification Scale to assess bleeding events.

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

- A fall in hemoglobin of 2 g/dL or more (if only hematocrit values are available, a 3% decrease will be equivalent to a 1 gram fall in hemoglobin), 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

Approach to Subjects with a Bleeding Event

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

Delay the next study drug administration, or discontinue treatment if indicated. Rivaroxaban has a plasma half-life of approximately 5 to 9 hours, and in some patients up to 13 hours. Therefore, temporary cessation of study drug may allow control of bleeding.

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

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

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

- Activated prothrombin complex concentrate (APCC)
- Prothrombin complex concentrate (PCC)
- Recombinant factor VIIa (NovoSeven®)
- Any products administered to control bleeding should be entered in the eCRF.

Note: Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. There is currently no scientific rationale for benefit, nor experience with systemic hemostatics (eg, desmopressin, aprotinin, tranexamic acid, epsilon amino caproic acid).

Adverse Events

Adverse events reported by the subject to the investigator will be recorded as specified in Section 12, Adverse Event Reporting.

Clinical Laboratory Tests

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

The following test results with reference ranges will be obtained from the hospital lab/local lab at the time of the index event:

- Hemoglobin
- Platelet count
- Serum Creatinine (creatinine clearance to be calculated by MDRD formula)
- Serum or urine pregnancy results for women of childbearing potential only
- BNP or NT-proBNP values
- If available, CK-MB and troponin values

9.5.2. Safety Outcomes

Overall safety will be assessed for bleeding using the following definitions:

- The principal safety outcome is the composite of fatal bleeding or bleeding into a critical space (intracranial, intraspinal, intraocular [vitreous or retinal], pericardial, retroperitoneal, intra-articular, intramuscular with compartment syndrome) with a potential for permanent disability.
- Additional bleeding outcomes are bleeding events requiring hospitalization, and ISTH major bleeding events.

9.6. Benefit-Risk Balance

Benefit-risk balance of rivaroxaban will be explored. Refer to Section 11.7, Benefit-Risk Analysis for details.

9.7. Sample Collection and Handling

Refer to the Time and Events Schedule for the timing and frequency of all sample collections.

Instructions for the collection, handling, and shipment of samples (to be collected after screening and sent to the central laboratory) are found in the laboratory manual that will be provided for sample collection and handling.

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form.

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 as having completed the double-blind treatment period if the subject continues taking double-blind study drug until either the GTED or within 7 days before the death of the subjects.

A subject will be considered as having completed the study if the subject (regardless of whether he/she continues on study drug) is followed according to the visit schedule until the EOS Visit or has died.

Subjects who are taking study drug up until the GTED is announced will stop taking study drug after taking their AM and PM doses on the GTED and return to the investigator for the EOS Visit (30±15 days, but no sooner than 15 days after the GTED).

10.2. Discontinuation of Study Treatment

If a subject's study treatment must be discontinued before the end of the double-blind treatment phase (ie, GTED), this will not result in automatic withdrawal of the subject from the study and the subject should continue to be followed for efficacy and safety outcome events. Study drug may be temporarily discontinued, or permanently discontinued. If study drug is permanently discontinued prior to GTED and the investigator or subject would like to resume study drug, this is permissible and the investigator's site manager should be contacted for instructions.

10.2.1. Temporary Discontinuation of Study Treatment

Study drug may be temporarily discontinued, however, these interruptions should be kept to a minimum as much as possible. There is no specific limitation to the duration of a temporary study drug discontinuation. Study drug should be temporarily discontinued if the subject:

- Undergoes PCI, CABG, any other interventional procedure (including minor procedures such as colonoscopy or dental extractions), or any other medical condition that may require temporary interruption or use of therapy due to bleeding risk or use of open-label anticoagulants.
- Requires use of an anticoagulant on a ***temporary basis*** (such as heparin or enoxaparin for ACS or PCI).
- Experiences a major bleeding event other than intracranial bleeding. For less severe bleeding events, investigator discretion is allowed. If possible study drug should be resumed when the bleeding event has resolved and the cause has been identified and corrected.
- Develops a new neurologic deficit or significant alteration in mental status. Once a diagnosis is made and appropriate treatment is provided, the study medication may be restarted at the discretion of the investigator.
- Develops a platelet count less than 50,000/μL.
- Has a serious adverse event that is considered by the investigator to be possibly related to, or exacerbated by, study drug administration.
- Requires a prohibited therapy on a temporary basis (see Section 8, Prestudy and Concomitant Therapy).

Study drug can be resumed when the investigator considers it safe to do so. Study drug need not be discontinued if the subject experiences one of the primary or secondary efficacy outcome events (except for hemorrhagic stroke or other intracranial bleeding). If a hemorrhagic stroke, or other intracranial bleeding occurs, the subject must be ***permanently discontinued*** from study drug.

If a subject temporarily discontinues study drug, and the GTED is announced prior to the subject resuming study drug, the subject will then be considered to have been ***permanently discontinued*** from study drug.

Discontinuation of Study Drug for Vascular Procedure

Clinical guidance regarding the bolus dose of antithrombin to administer by translating peak factor Xa inhibition with oral rivaroxaban to peak factor Xa inhibition with subcutaneous enoxaparin can be found in Attachment 3 and Attachment 4. These comparative tables depict the approximate equivalent dose of subcutaneous enoxaparin (mg/kg) relative to a given dose of rivaroxaban at a given time following its administration and should assist the investigator in deciding which dose of enoxaparin or equivalent dose of another antithrombotic agent to administer in the event when a subject may have to undergo an emergency interventional coronary procedure or pharmacologic reperfusion while receiving study drug. If an urgent revascularization is required, consider i.v. administration of 0.5 mg/kg of enoxaparin or its antithrombotic equivalent in subjects who undergo PCI. Subjects in whom administration of fibrinolytics is considered may require unblinding if the last dose of study drug was taken less than 6 hours before initiation of reperfusion therapy. Refer to Attachment 3 and Attachment 4 for guidance.

In the event that a subject requires a non-emergency revascularization procedure (PCI or CABG), study drug should be stopped approximately 12 hours before the procedure, if possible, and appropriate anticoagulant or antiplatelet therapy should be instituted as medically indicated. Once the subject has recovered from the PCI or CABG, and assuming no ongoing bleeding risk is present, the subject may, at the discretion of the physician, resume study drug approximately 12 hours after the arterial sheath has been removed (subjects with PCI) or the post-procedural drains (subjects with CABG surgery) have been removed and the last dose of parenteral anticoagulant therapy has been administered, whichever is later.

10.2.2. Permanent Discontinuation of Study Treatment

If a subject must be permanently discontinued from study drug before the end of the double-blind treatment period, this will not result in automatic withdrawal of the subject from the study, and the subject should continue to be followed for efficacy and safety outcome events.

A subject should be discontinued from study drug if:

- The investigator believes that for safety reasons (i.e., adverse event) it is in the best interest of the subject to stop study drug.
- The subject becomes pregnant.
- The subject develops any condition which requires permanent anticoagulation (eg, DVT, PE, atrial fibrillation [$CHADS_2 = 2$ or higher]).
- The subject has a sustained fall in eGFR to below 20 mL/min (by MDRD method). This can be obtained by using the IWRS and entering a recent local serum creatinine obtained from the subject.

- The subject requires hemofiltration or dialysis on a permanent basis
- The subject requests to discontinue study drug permanently
- The subject has a hemorrhagic stroke, or intracranial bleeding
- The subject has a heart transplant

If a subject discontinues study treatment permanently before the end of the double-blind treatment phase (ie, GTED), the Early Permanent Study Drug Discontinuation assessments as outlined in the TIME AND EVENTS SCHEDULE should be conducted.

Because the primary analysis of the study is based upon the ITT population, a subject who permanently discontinued study drug treatment should return for all subsequent site visits and procedures until the study ends. If a subject is unwilling or unable to return for follow-up visits in person, sites should attempt to collect as much follow-up visit information as possible, including contacting the subject regularly by telephone or by mail to determine vital status and if an outcome event has occurred, until the GTED, as agreed to by the subject during the initial informed consent process. Collection of study outcome events and vital status information until the announced GTED is critical for this study because the primary analysis of the study is based upon the ITT population. Once the GTED is announced the subjects who have prematurely discontinued study drug will return to the site (or at least be contacted by telephone) to complete the EOS Visit 30±15 days after the GTED. If the subject cannot physically return to the office, a telephone contact should be made to collect the required information in lieu of the office visit. If applicable, subjects' medical or public records may be reviewed unless this contact is not allowed by local regulations.

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

The eCRF is to be completed to identify the reason for permanent discontinuation of study drug. If study drug is terminated for a serious adverse event, expedited reporting (within 24 hours) is also required as outlined in Section 12.3.2, Serious Adverse Events.

10.3. Withdrawal From the Study

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

- Lost to follow-up (only after all means of all subsequent contact, including locator services where permitted by law, up until the EOS visit, will lost to follow up be declared).
- Withdrawal of consent (unless specifically refused by the subject, subject contact will be made to obtain vital status at the EOS visit).

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

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

If a subject withdraws from study or is lost to follow-up, his or her vital status will be collected at the EOS visit either by telephone or in person, or if applicable, by a review of the subject's medical or public records unless this contact is not allowed by local regulations.

Withdrawal of Consent for the Use of Samples in Future Research

A subject may withdraw their consent for biomarker (D-dimer) samples to be used for future research. In this case, samples will be destroyed only after they are no longer needed for the main study.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

The primary study objective will be addressed by comparing distribution of time to the first occurrence of a primary efficacy endpoint between treatment groups. Specifically, the following primary statistical hypotheses will be tested.

> Null hypothesis H_0: there is no difference between treatments in distribution of time from randomization to the first occurrence of the primary efficacy endpoint event.
>
> Alternative hypothesis H_A: The distributions of time from randomization to the first occurrence of the primary efficacy endpoint event are different between the 2 treatment groups.

Analysis methods and decision rules are outlined in Section 11.3 below.

11.1. Analysis Populations and Observational Periods

Definition of an analysis data set contains these 2 elements: 1) *subject population*, which specifies which subjects will be included in an analysis; and 2) *observational period*, which specifies the time window within which data will be included in an analysis. Key subject populations and observational periods are defined below.

Subject Population

Intention-to-treat (ITT) population: This subject population consists of all randomized subjects with valid informed consent.

Per-protocol (PP) population: this population is a subset of the ITT population. Subjects with major protocol deviations will be excluded from PP population. Major protocol deviations will be defined in the Statistical Analysis Plan (SAP).

Safety population: this population is a subset of the ITT population, consisting of all randomized subjects who receive at least one dose or partial dose of study drug.

Observational Period

Up–to-GTED: this observational period includes all data from randomization to the global treatment end date, inclusively.

On-treatment: this observational period includes data from the first dose of study drug to 2 days after the last dose of the study drug, inclusively.

Post-randomization: this observational period includes all data from randomization to the last contact.

Post-first dose of study medication: this observational period includes all data from the first dose of study medication to the last contact.

11.2. Sample Size Determination

This is an event driven study. The study was initially designed to observe occurrences of the primary efficacy event in 984 unique randomized subjects, on or before the GTED, to have 90% power to detect a 20% relative risk reduction (RRR, defined as subtracting the hazard ratio [test to control] from 1) in the composite of ACM, MI, or stroke at a 5%, 2-sided significance level. A total of approximately 5,000 subjects will be randomized to either the rivaroxaban group or the placebo group in a 1:1 ratio. If the event rate is lower than expected, the sample size may be increased by up to 500 subjects.

The above sample size calculation was estimated based on the following assumptions.

- Effect size: 20% RRR
- Event rate in the placebo arm: 19%/year
- Power: 90%
- Over all α level: 5%, 2-sided
- Permanent premature treatment discontinuation rate: 10%/year
- Lost-to-follow-up: 1%/year
- Duration of enrollment period: 24 months (based on a non-uniform enrollment distribution. The distribution will be described in the SAP.)
- Duration of study (from First-Patient-Randomization to GTED): 31 months

The assumptions of RRR and event rate are based on observations from subjects with congestive HF (the HF subgroup) in the ATLAS ACS 2 TIMI 51 study and review of literature. Observed data from the HF subgroup in study ATLAS ACS 2 TIMI 51 are summarized in Table 1. Note that the study population in this study is slightly different from the HF subgroup in the ATLAS ACS 2 TIMI 51 study. The subject population in the present study will have HF with significant CAD.

Based on historical data, the mortality rate in this study was expected to be higher than the observed mortality rate in TIMI 51 ATLAS 2 study. Therefore, an event rate of 19%/year was used in sample size calculation.

The study is revised to observe occurrences of the primary efficacy event in 1,200 unique randomized subjects based on a blinded simulation study performed on currently available trial data (ie, longer enrollment period, lower than anticipated primary efficacy event rate, higher than anticipated study drug discontinuation rate). Further details are described in the SAP.

An interim analysis will be conducted when the primary efficacy events are observed in approximately 600 unique subjects (see Section 11.9 for more details).

11.3. Efficacy Analyses

Primary Endpoint

The primary efficacy analysis endpoint is the time from randomization to the first occurrence of death, MI, or stroke. The associated statistical null hypothesis is that there is no difference between treatment groups in distribution of the time, and the alternative hypothesis is that there is a difference between treatment groups.

The primary statistical hypothesis will be tested using a log-rank test, stratified by region. In addition to the final analysis, the primary statistical hypothesis will be tested in an interim analysis when approximately 600 primary efficacy events are observed. The primary analysis will be based on the analysis set defined by ITT subject population and the up-to-GTED observational period (up to the cut-off date to be specified for the interim analysis). Subjects will be analyzed according to the treatment group to which they are randomized, regardless of actual treatment received. The overall α level is 5%, 2-sided. A Lan-DeMets α spending function with O'Brien-Fleming type of boundaries will be used to preserve the overall type I error rate. If the log-rank test statistics crosses the stopping boundary, and the log-rank statistic is less than 0, ie, the observed number of events in the rivaroxaban group is less than the expected number of events under the null hypothesis, it will be concluded that the study has demonstrated that efficacy of rivaroxaban is superior to that of placebo in prevention of ACM, MI, and stroke.

It is expected that risk of death will be the highest shortly after discharge from the index events. Therefore, the cumulative event rate derived from Kaplan-Meier estimate will be displayed graphically to evaluate the timing of event occurrence and the consistency of the treatment effect over time.

The RRR will be estimated using a Cox proportional hazards model, stratified by region, with treatment (as randomized) as the only covariate. The point estimate and corresponding 95% confidence interval (CI) for the hazard ratio (HR, rivaroxaban to placebo) will be reported. The plausibility of proportional hazards assumption will be assessed by visually comparing the plot of the log of cumulative hazard between treatments, and formally tested by adding a treatment by logarithm-transformed time interaction into the Cox model. A p-value greater than 0.05 for the interaction term will be interpreted as no evidence against the proportional hazard assumption.

A number of sensitivity analyses will be conducted to assess the robustness of the primary efficacy analysis. These include a log-rank test stratified by country, an unstratified log-rank test, repeating analyses mentioned above for analysis set defined by the on-treatment observational period and the per-protocol subject population, and analysis set defined by the post-randomization observational period and the ITT subject population. Additional sensitivity analyses will also be conducted based on subject populations enrolled under various versions of the protocol amendments. Additional post-hoc analyses may be conducted to investigate unexpected results.

Relative risk reductions on components of the primary efficacy endpoint will be evaluated using a Cox proportional hazards model as described above.

Extensive efforts will be made to collect complete data for all subjects randomized in this study. Subjects will be followed up to the end of the study and will complete all required data collection, regardless of their compliance with study drug or visits. For subjects who are lost to follow up or withdraw consent, efforts will be made to obtain their vital status at the end of study from permitted sources.

Efforts will be made to clean up the missing or partially missing event date for primary and secondary efficacy endpoints, as well as key safety endpoints, before database lock. Imputation rules for the missing or partially missing date will be specified in SAP.

Homogeneity of treatment effects, both in RRR and direction, in the following subgroups will be assessed by subgroup analysis. Analysis methods will be detailed in SAP.

- Age (< 65 vs ≥ 65; < 75 vs ≥ 75 years)
- Sex (men vs women)
- LVEF (≤30% vs > 30%; ≤ median vs > median)
- Estimated glomerular filtration rate (Modification of Diet in Renal Disease formula value <30, 30 to <60, 60 to <90, ≥90 mL/min/1.73 m^2)
- Baseline D-dimer level by quartile
- BNP, NT-proBNP (≤ median vs > median)
- History of diabetes (yes vs no)
- History of stroke (yes vs no)
- History of MI (yes vs no)
- Hypertension (yes vs no)
- Body Mass Index (<25, 25 to <30, ≥30 kg/m^2)
- Baseline digoxin use (yes vs no)
- Baseline β-blocker use (yes vs no)
- Baseline aldosterone inhibitors (yes vs no)

- Baseline ACEI or ARB (yes vs no)
- Baseline aspirin use (yes vs no)
- Baseline aspirin vs dual antiplatelet use
- Baseline thienopyridine use (yes vs no)
- NYHA (Class II, III, IV)
- Race (White vs others)
- Race (White, Asian, other)
- Region

Secondary Endpoints

If superiority of rivaroxaban over placebo in reducing the risk of the primary efficacy endpoint is established, treatment effects in secondary endpoints will be tested subsequently in the hierarchical order:

1) Composite of CV mortality or re-hospitalization for worsening of HF
2) CV mortality
3) Re-hospitalization for worsening of HF
4) Re-hospitalization for CV events

Statistical significance is required before testing the next hypothesis in the hierarchical test procedure. These secondary endpoints will be analyzed using time-to-event analysis described above for the primary endpoint. Details will be provided in the SAP.

Exploratory Endpoints

Analysis methods and results for MRU data will be provided in a separate report. Due to the nature of exploration and consideration regarding to type I and type II errors, no statistical testing will be conducted for symptomatic DVT and PE. However, the size of treatment effects on these endpoints will be estimated using a Cox proportional hazards model, with treatment is the only covariate. HRs and 95%CIs will be reported.

11.4. Biomarker Analyses

Descriptive summary statistics will be provided for baseline D-dimer level and change from baseline at Week 4 visit. Descriptive summary statistics will be provided for baseline BNP and NT-proBNP.

11.5. Medical Resource Utilization Analyses

Analysis methods and results will be described in a separate report.

11.6. Safety Analyses

Bleeding Events

The principal safety evaluation endpoint for this study is the composite of fatal bleeding, or bleeding into a critical space with potential for permanent disability. Time to the first occurrence of the principal safety endpoint will be compared using a Cox proportional hazards ratio model, stratified by region, with treatment as the only covariate. The primary analysis will be conducted for analysis set defined by the on-treatment observational period and the safety population. Subjects will be analyzed according to the study drug assigned.

In addition, time to the following bleeding events will be analyzed using the same method.

- Bleeding requiring hospitalization
- ISTH major bleeding event

The safety outcomes will also be analyzed for other observational periods as defined in the SAP.

In addition, summary statistics will be provided for all other reported bleeding events.

Adverse Events

Because the safety profile of rivaroxaban has been well established in previous large and extensive trials, this study will collect limited adverse event data. For adverse events that are collected as specified in Section 12, ADVERSE EVENT REPORTING, the verbatim terms reported in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). For each MedDRA preferred term, the percentage of subjects who report at least 1 occurrence of the given event will be summarized by treatment group. Additional summaries, listings, or subject narratives may be provided, as appropriate.

Clinical Laboratory Tests

Because the safety profile of rivaroxaban has been well established in previous trials, this study will not collect laboratory data routinely. There is no plan to analyze laboratory data. Local lab data may be discussed in subject narratives.

11.7. Benefit-Risk Analysis

Benefit-risk of rivaroxaban vs placebo will be evaluated based on the excess number of events between treatments for events intended to be prevented (benefits) and events that may be caused (risks). Excess number of events is defined as the difference in event rate times a hypothetical population size (e.g., 10,000 patients or person-years). The event rate will be calculated based on time-to-first event approach as the following:

- Person-year rate, expressed as number of events per 100 person-years exposure time
- Kaplan-Meier Product-Limit estimates of cumulative event rates at 1-year

The primary benefit-risk analysis will be based on a comparison between events that are fatal or are likely to cause irreversible harm, where the endpoints are defined to avoid double-counting an event as both a benefit and as a risk:

Benefits

Composite of non-bleeding related death, non-fatal MI, or non-fatal ischemic stroke

- Non-bleeding related death
- Non-fatal MI
- Non-fatal ischemic stroke

Risks

Composite of fatal bleeds, non-fatal intracranial hemorrhage, or other non-fatal critical organ bleeds

- Fatal bleeds
- Non-fatal intracranial hemorrhage
- Other non-fatal critical organ bleeds (intraspinal, intraocular [vitreous or retinal], pericardial, intra-articular, retroperitoneal, intramuscular)

The primary analysis for benefit-risk evaluation will be based on the ITT analysis population, in the up-to-GTED observational period. All comparisons between treatments will be based on the excess number of events (as defined above) and the corresponding 95% confidence intervals will be provided.

11.8. Independent Data Monitoring Committees

An IDMC will be established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study and to meet efficacy objectives. The IDMC will review unblinded safety data periodically. If necessary or requested by the IDMC, subject level unblinded data may be provided to the IDMC. In addition, the IDMC will review results of the planned interim analysis (see Section 11.9 for more details) and make recommendation whether the study should be terminated prematurely due to overwhelming benefit or futility.

The IDMC will consist of at least one medical expert in the relevant therapeutic area and at least one statistician. The IDMC will be supported by an independent statistical group which is not involved with the study otherwise. All unblinded data will be handled by this statistical group until the completion of the study. In their first meeting the committee will decide the frequency of future meetings, the scope of safety review, elect a chair person, and finalize the charter. Detailed IDMC responsibilities, authorities, decision guidelines, and procedures will be documented in its charter.

11.9. Interim Analysis

An interim analysis will be conducted when primary efficacy events have been observed in approximately 600 subjects. A log-rank test, stratified by region, will be employed to compare the distribution of time to the occurrence of the composite primary efficacy endpoint between the 2 treatment groups. If all the following conditions are met, the IDMC may recommend terminating study early:

- the log-rank test statistic crosses the stopping boundary, and
- the 2-sided p-value for all-cause mortality is less than 0.05, and
- the totality of data suggests an overwhelming benefit of rivaroxaban over placebo

On the other hand, if the conditional power (based on the assumption that the RRR in the remaining study is 20%) is 10% or lower, the study may be stopped for futility. Detailed stopping guideline will be specified in the IDMC charter.

The Lan-DeMets α spending function approach with O'Brien-Fleming type of boundaries will be used in the interim analysis. The α spent in the interim analysis is 0.003 with a corresponding critical value of 2.936 (East®, Version 5.3, Cytel Inc.). If the study continues beyond the first interim look, the critical value for the final analysis is 1.969. The actual α spent and corresponding critical values may slightly vary from aforementioned numbers, depending on the actual number of events included in the interim analysis. If the test statistic for the primary efficacy endpoint crosses the stopping boundary, the secondary endpoints will be statistically tested in the hierarchical order as specified in Section 11.3. This group sequential test procedure will control the type I error rate. There will be no adjustment for p-values in the final study report.

12. ADVERSE EVENT REPORTING

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

Rivaroxaban has been extensively studied in Phase 1 through Phase 3 clinical studies involving more than 70,000 patients and its overall adverse event profile has been well described. Appropriate information concerning adverse events were systematically collected and submitted to regulatory authorities. For the purposes of this study (and after discussion with appropriate regulatory agencies) certain non-serious adverse events will not be collected, while certain events will be collected as endpoints and therefore not reported as serious adverse events. All data on safety and outcomes will be reviewed regularly by an unblinded IDMC. This will be explained in Section 12.3.1, All Adverse Events.

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

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per 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 required adverse events starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

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

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires a minimum of 24 hours of hospitalization or prolongation of existing hospitalization, which may include time spent both in the ER, and the In-Patient Room
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

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

For the purposes of this study, efficacy and safety outcome events will not be considered as adverse events or serious adverse events (See Section 12.3.1, All Adverse Events). If a serious and unexpected non-CV adverse event occurs for which there is evidence suggesting a causal

relationship between the study drug and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study outcome (eg, all-cause mortality).

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.

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 below in Section 12.1.2.

12.1.2. Attribution Definitions

Not Related

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

Doubtful

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

Possible

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

Probable

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

Very Likely

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

12.1.3. Severity Criteria

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

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

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

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

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

12.2. Special Reporting Situations

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

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

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

12.3. Procedures

12.3.1. All Adverse Events

For the purposes of this trial the following outcome events **will not** be considered as adverse events or serious adverse events. These events will be captured on the eCRF and in the database as outcomes only and will be waived from unblinding and exempted from expedited reporting:

- CV death
- MI
- stroke
- venous thromboembolism (DVT and PE)
- hospitalization for heart failure
- any CV hospitalization
- unstable, worsening, and new angina pectoris
- resuscitated cardiac arrest
- bleeding events – note that bleeding events requiring medical attention/hospitalization will be entered on the bleeding page of the eCRF, refer to Section 9.5.1 under Bleeding

Outcome Evaluations; any bleeding event leading to permanent study drug discontinuation will also be entered on the bleeding page of the eCRF.

- CV signs or symptoms expected or anticipated in this population such as cardiac arrhythmia, chest pain, dyspnea, edema, ACS, and TIAs

The following adverse events or serious adverse events will be collected and entered into the eCRF, unless they are considered outcome events as specified in the list above. The serious adverse events need to be reported to the sponsor within the appropriate timeline as described in Section 12.3.2, Serious Adverse Events.

- Adverse events leading to permanent study drug discontinuation
- All non-CV serious adverse events
- Common drug-induced reactions including but not limited to the following adverse events should be considered serious:
    - Suspected toxic effect on the bone marrow including severe thrombocytopenia (platelet count less than 50,000/mL), severe neutropenia (white blood cell count less than 500/mL), pancytopenia, aplastic anemia
    - Suspected hypersensitivity reaction (e.g., anaphylaxis, angioedema, severe urticaria, bronchospasm, etc.)
    - Severe skin reactions such as Stevens-Johnson Syndrome
    - Suspected severe liver injury

While one of the primary outcome measures is ACM, any non-CV death (eg, traumatic bleeding events resulting in death are considered to be non-CV events) will be reported as a serious adverse event.

All adverse events and special reporting situations, 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. If any outcome event or adverse event occurs from the time a signed ICF is obtained until randomization, this event will be recorded as an adverse event or an SAE on the eCRF. The last expected visit when adverse events will be collected is during the EOS visit [the visit following GTED, which can take place 30±15 days after GTED]).

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

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all serious adverse events that are unlisted (unexpected) and associated with the use of the study drug. The investigator (or sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

12.3.2. Serious Adverse Events

All non-CV serious adverse events occurring during clinical studies 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 member of the study-site personnel, 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)

Any non-CV event that occurs during the course of a subject's participation in the study which requires a minimum of 24 hours of hospitalization (or prolongation of hospitalization), including time spent both in the ER, and the In-Patient Room, must be reported as a serious adverse event, except hospitalizations for the following:

- Social reasons in the absence of an adverse event
- Surgery or procedure planned before entry into the study

12.3.3. Pregnancy

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

Event Form. Any subject who becomes pregnant during the study must discontinue further study treatment.

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

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

12.4. Contacting Sponsor Regarding Safety

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

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. PQCs 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 Drugs

The study drug supplied for this study is rivaroxaban 2.5 mg and matching placebo provided as round yellow tablets. Refer to the Investigator's Brochure for a list of excipients.

14.2. Packaging

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

14.3. Labeling

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

14.4. Preparation, Handling, and Storage

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

14.5. Drug Accountability

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

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug, and study drug returned by the subject, must be available for verification by the sponsor's 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 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 delegated and qualified member of the study-site personnel, or hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the assigned study site agreed upon with the sponsor. Study drug may not be transported from one site to another.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator Brochure
- Pharmacy manual/site investigational product manual

- IWRS Manual
- eDC Manual

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study and provide their consent voluntarily will be enrolled.

While no study has definitively proven the benefit of anticoagulation in HF patients with CAD after decompensation of their HF, data from a large subgroup of subjects in the rivaroxaban ATLAS ACS 2 TIMI 51 study suggest a benefit in reduced risk of death in subjects with ACS and heart failure. While ACS subjects will not be included in this study, those included will have significant CAD. A placebo control group is considered appropriate as anticoagulation in this type of patient has not been definitively proven effective in reducing the risk of death, MI, or stroke. In addition, all subjects will be receiving standard HF therapy, including antiplatelet therapy where appropriate.

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

Subjects will be strongly encouraged to remain in the clinical study should their study drug be discontinued prematurely due to an adverse event, or other reasons, in order to assess the vital status and determine if outcome events may have occurred. If these subjects refuse office visits, the investigator is asked to encourage the subjects to allow regular contact (eg, by telephone) until study end, according to the TIME AND EVENTS SCHEDULE, either with them, or with a close friend or relative, or their primary care physician to determine vital status and if an efficacy or safety outcome event has occurred.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the clinical 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 principals that originated in the Declaration of Helsinki, and that the clinical study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

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

- Final protocol and, if applicable, amendments
- Sponsor-approved informed consent form (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), the informed consent form, 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
- Revision(s) to informed consent form 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 investigational 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
- Annual Safety 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 trial conduct), the amendment and applicable informed consent form 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 clinical study. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct).

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

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form that is 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 principals 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 staff without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By

signing the informed consent form the subject is authorizing such access, and agrees to allow his/her study physician or health authorities to re-contact the subject for the purpose of obtaining consent for additional safety evaluations, if needed to obtain information about his or her survival status. Where permitted by law, a locator may be used.

The subject will be given sufficient time to read the informed consent form 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 informed consent form must be given to the subject.

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

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 DNA, pharmacodynamic, biomarker, PK, or immunogenicity 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 Storage of Samples for Future Research

Biomarker samples collected in this study will be stored for up to 1 year following the completion of the last subject for the study (or according to local regulations). Samples will be used for exploratory evaluations of the effects of rivaroxaban on D-dimer levels and its potential relationship to responders in this heart failure study. The research may begin at any time during the study or the post-study storage period.

Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.3, Withdrawal From the Study (Withdrawal From the Use of Samples in Future Research).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

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

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

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

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

17.2.2. Required 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

17.3. 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 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 CRF: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable. Inclusion/Exclusion criteria should be documented with the PI or authorized delegate signature that the subject is eligible for participation.

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 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 CRF and will be considered source data:

- Race
- History of smoking
- Blood pressure and pulse/heart rate
- Height and weight

17.5. Case Report Form Completion

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

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

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

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

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

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

- Study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool)
- Study site manager can generate a query for resolution by the study-site personnel
- Clinical data manager can generate a query for resolution by the study-site personnel

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review CRFs for accuracy and completeness during on-site monitoring visits and after 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 CRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

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

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

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

17.8. Monitoring

A streamlined approach to monitoring will be implemented in this study that utilizes an algorithm to analyze data query rates to identify sites requiring additional training, and remote data surveillance that monitors subject characteristics, events and clinical and laboratory data at the level of each participating site. This seems particularly appropriate since the primary efficacy outcome for this study is the clinical composite outcome of ACM, stroke or MI, and not a surrogate outcome.

The sponsor will perform on-site monitoring visits as frequently as necessary with all sites being monitored at least at the start and at the end of the study. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. At these visits, the monitor will compare the data entered into the CRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel. Monitors will also review all source documentation which will be used for verification of protocol specified event outcomes based on pre-defined criteria (see Outcome Event Definitions with Section 9.2.1)

Remote data surveillance will be performed in multiple ways. First, a control based statistical process predicated on a set of predefined parameters (eg, the mean number of critical queries generated from the CRF per subject per day of the study, the number of missing forms per subject) will be calculated and a pre-specified upper limit will be defined for these parameters over time. Sites that exceed the upper limit for these parameters during a specified observational period may be subject to an additional monitoring visit. Second, the decision to monitor a site will be made following review of clinical demographic data, key site performance data (such as time to enter CRF data, time to report serious adverse events) and key outcome variable data. Key subject demographic data, site performance data, and key outcome data will be monitored remotely as part of routine data surveillance on a monthly basis for all sites and be compared to the results seen overall for that country and region. Sites identified as having subjects with data that deviates substantially from the norm may also be subject to additional in-person monitoring visits, and these data will be used to supplement the data from the statistical process control for reviewing query generation.

Remote monitoring of scanned or faxed imaging reports, laboratory results and other source documents will be used by the monitors, local trial managers and other clinical staff on an ongoing basis to also verify protocol specified events outcomes based on pre-defined criteria (see Outcome Event Definitions with Section 9.2.1).

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.

17.9. Study Completion/Termination

17.9.1. Study Completion

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

17.9.2. Study Termination

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development

17.10. On-Site Audits

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

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

17.11. Use of Information and Publication

All information, including but not limited to information regarding rivaroxaban or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory 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 clinical study will be used by the sponsor in connection with the continued development of rivaroxaban, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain CRF data from all study sites that participated in the study, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's database. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. 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: The MDRD Formula for Calculation of GFR

The Modification of Diet in Renal Disease (MDRD) study was a multicenter, controlled trial that evaluated the effect of dietary protein restriction and strict blood pressure control on the progression of renal disease.1 During the baseline period, serum creatinine and several variables were measured in 1,628 patients with chronic renal disease. The objective was to develop an equation that would predict GFR.

From this study, it was determined that older age and female sex were independent predictors of GFR, reflecting the well-known relation of age and sex to muscle mass. GFR was further adjusted for body surface area so that neither height nor weight was an independent predictor of adjusted GFR. African American ethnicity was an independent predictor of higher GFR as on average, black persons have greater muscle mass than whites.

The final MDRD Study prediction equation for GFR is as follows with Pcr being serum or plasma creatinine in mg/dL:

$$GFR\ (mL/min/1.73\ m^2) = 186 \times (Pcr)^{-1.154} \times (age)^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African American})$$

The GFR is expressed in $mL/min/1.73m^2$.

For this study the MDRD GFR will be calculated upon randomization and as needed by the IWRS, dependent upon variables provided by the investigative sites.

1. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med. 1999; 130:461-470.

Attachment 2: Modified Rankin Scale

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms: able to carry out all usual duties and activities
2	Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance
3	Moderate disability: requiring some help, but able to walk without assistance
4	Moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability: bedridden, incontinent and requiring constant nursing care and attention
6	Patient death

Attachment 3: Enoxaparin Equivalent Doses for Given Rivaroxaban Doses

Equivalent SQ Dose of Enoxaparin in mg/kg For a Given Dose of Rivaroxaban and a Given Time Following Its Administration		
Time	**Placebo**	**2.5 mg Rivaroxaban**
3 h	0	0.15 mg/kg
6 h	0	0.1 mg/kg

For example, this table would be interpreted to mean that 3 hours after a 2.5 mg dose of rivaroxaban, the anticoagulation status would be similar to 0.15 mg/kg of enoxaparin at that 3 hour time point. If additional enoxaparin is needed, the dose would be the desired dose minus the dose provided in the table at the specific time point. In the example above for the 0.5 mg/kg dose of enoxaparin at 3 hours following a rivaroxaban dose, the dose of enoxaparin would be 0.35 mg/kg (0.5 – 0.15 mg/kg).

Attachment 4: Approach to Subjects Requiring Thrombolysis: Administration of an Adjusted Enoxaparin Dose

Approach to the Subject Requiring Thrombolysis		
If a subject requires thrombolysis, it may be necessary to unblind the subject and administer a reduced enoxaparin dose with the adjustment in mg/kg shown below:		
Subjects who are less than 6 hours from the last dose of study medication may need to be unblinded at the discretion of the investigator (refer to the shaded zone of the table). Do not unblind subjects who fall into the white zone and treat with full dose antithrombin (0.5 mg/kg enoxaparin or equivalent):		
Time	**Placebo**	**2.5 mg Rivaroxaban**
3 h	0	**0.15 mg/kg**
6 h	0	0.1 mg/kg
9 h	0	0

For example, this table would be interpreted to mean that 3 hours after a 2.5 mg dose of rivaroxaban, the anticoagulation status would be similar to 0.15 mg/kg of enoxaparin at that 3 hour time point. If additional enoxaparin is needed, the dose would be the desired dose minus the dose provided in the table at the specific time point. In the example above for the 0.5 mg/kg dose of enoxaparin at 3 hours following a rivaroxaban dose, the dose of enoxaparin would be 0.35 mg/kg (0.5 – 0.15 mg/kg).

INVESTIGATOR AGREEMENT

JNJ-39039039; BAY 59-7939 (rivaroxaban)
Clinical Protocol RIVAROXHFA3001 Amendment INT-3

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): William Byra, MD

Institution: Janssen Research & Development

Signature: [redacted] Date: 2/17/2016

(Day Month Year)

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

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Approved, Date: 1 December 2016